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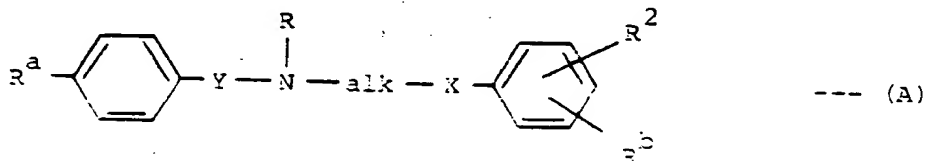
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ANTIARRHYTHMIC AGENTSBackground of the Invention

This invention relates to certain sulfonamides which are antiarrhythmic agents, and to intermediates therefor.

The antiarrhythmic compounds of the invention prolong the duration of the action potential in cardiac muscle and conducting tissue, and thereby increase refractoriness to premature stimuli. Thus, they are Class III antiarrhythmic agents according to the classification of Vaughan Williams (Anti-Arrhythmic Action, E.M. Vaughan Williams, Academic Press, 1980). They are effective in atria, ventricles and conducting tissue both in vitro and in vivo and are therefore useful for the prevention and treatment of a wide variety of ventricular and supraventricular arrhythmias including atrial and ventricular fibrillation. Because they do not alter the speed at which impulses are conducted, they have less propensity than current drugs (mostly Class I) to precipitate or aggravate arrhythmias, and also produce less neurological side effects. Some of the compounds also have some positive inotropic activity and therefore are particularly beneficial in patients with impaired cardiac pump function.

Thus the invention provides compounds of the formula:-

Summary of the Invention

and their salts,

wherein R^a is $-\text{NO}_2$, $-\text{NH}_2$ or $-\text{NHSO}_2\text{R}^1$ where R^1 is a C_1 - C_4 alkyl group;

R^b is $-\text{NO}_2$, $-\text{NH}_2$ or R^3 where R^3 is $-\text{NHSO}_2(\text{C}_1$ - C_4 alkyl) or $-\text{CONR}^4\text{R}^5$ where R^4 and R^5 are each independently H or C_1 - C_4 alkyl or together with the nitrogen atom to which they are attached represent a 1-pyrrolidinyl,

piperidino, morpholino or N-methylpiperazin-1-yl group;

with the proviso that when one of R^a and R^b is $-\text{NO}_2$, then the other is not $-\text{NH}_2$;

X is O, S or a direct link;

Y is an ethylene group optionally substituted by a methyl group;

"alk" is an ethylene, trimethylene or tetramethylene group, "alk" being optionally substituted by a methyl group;

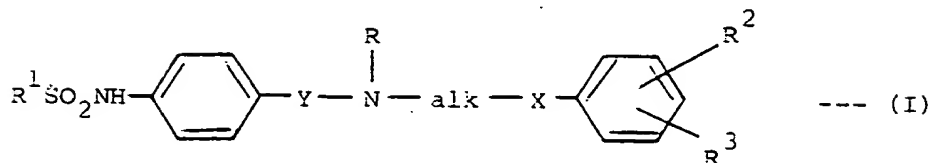
R is C_1 - C_4 alkyl;

and R^2 is H, halo, CF_3 or C_1 - C_4 alkyl.

Formula (A) includes compounds which are antiarrhythmic

agents, and compounds which are synthetic intermediates useful in the preparation of these antiarrhythmic agents. Those compounds having antiarrhythmic activity have the formula (I) set out below: the remaining compounds are synthetic intermediates only.

The invention thus provides antiarrhythmic agents of the formula:-



and their pharmaceutically acceptable salts,

wherein R and R^1 are each independently C_1-C_4 alkyl;

X is O , S or a direct link; ---

Y is an ethylene group optionally substituted by a methyl group;

"alk" is an ethylene, trimethylene or tetramethylene group, "alk" being optionally substituted by a methyl group;

R^2 is H , halo, CF_3 or C_1-C_4 alkyl;

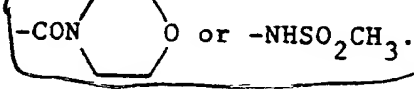
and R^3 is a group of the formula $-NHSO_2(C_1-C_4 \text{ alkyl})$ or $-CONR^4R^5$ wherein R^4 and R^5 are each independently H or C_1-C_4 alkyl or together with the nitrogen atom to which they are attached represent a 1-pyrrolidinyl,

piperidino, morpholino or N -methylpiperazin-1-yl group.

"Halo" means F , Cl , Br or I . C_3 and C_4 alkyl groups can be straight or branched chain.

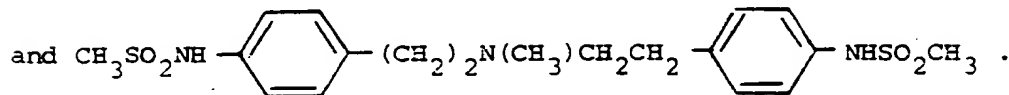
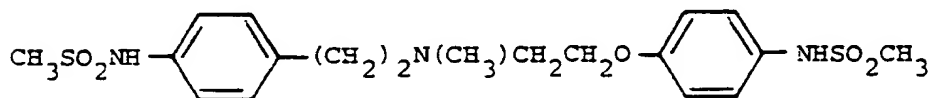
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R is preferably CH_3 or C_2H_5 , most preferably CH_3 . R^1 is preferably CH_3 . Examples of "alk" are $-(\text{CH}_2)_n-$ where n is 2, 3 or 4, $-\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)-$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2-$ and $-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)-$. "Alk" is preferably $-(\text{CH}_2)_n-$ where n is 2, 3 or 4, $-\text{CH}(\text{CH}_3)\text{CH}_2-$ or $-\text{CH}_2\text{CH}(\text{CH}_3)-$. "Alk" is most preferably $-(\text{CH}_2)_2-$. X is preferably O. Y is preferably $-(\text{CH}_2)_2-$. R^2 is preferably H, CH_3 or Cl. R^2 is most preferably H. R^3 is

preferably $-\text{CONH}_2$, $-\text{CONHCH}_3$, $-\text{CON}(\text{C}_2\text{H}_5)_2$, $-\text{CON}$  or $-\text{NHSO}_2\text{CH}_3$. R^3 is most preferably $-\text{NHSO}_2\text{CH}_3$.

One preferred group of compounds has the formula (I) as defined above wherein R , R^1 , R^2 , R^3 and "alk" are as defined for formula (I), Y is $-(\text{CH}_2)_2-$, and X is O or S. Another preferred group has the formula (I) wherein R , R^1 , R^2 , R^3 and "alk" are as defined for formula (I), X is a direct link, and Y is $-(\text{CH}_2)_2-$.

The preferred individual compounds have the formulae:-



The first method compound is the most preferred.

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Thus the present invention provides a pharmaceutical composition comprising a compound of the formula (I) as defined above or pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

5 The invention also provides a method of preventing or reducing cardiac arrhythmias in a human being, which comprises administering to said human an effective amount of a compound of the formula (I) or pharmaceutically acceptable salt thereof, or of a pharmaceutical composition as defined above.

10 The invention yet further provides a compound of the formula (I) or a pharmaceutically acceptable salt thereof, for use as a medicament, particularly as an antiarrhythmic agent.

15 The invention also provides the use of a compound of the formula (I), or of a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the prevention or reduction of cardiac arrhythmias.

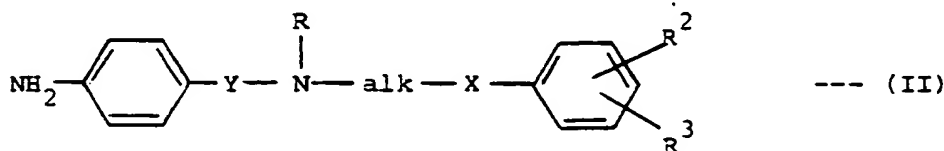
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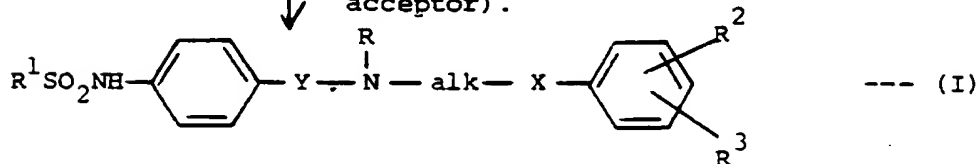
Detailed Description of the Invention

Route I

The compounds of the formula (I) can be prepared by the following general route, in which R, R¹, R², R³, alk, X and Y are as defined for formula (I). It starts from a compound in which R^a is -NH₂:-



↓
 Acylation using, e.g.,
 (R¹SO₂)₂O, R¹SO₂Cl
 or R¹SO₂Br (optionally in
 the presence of an acid
 acceptor).



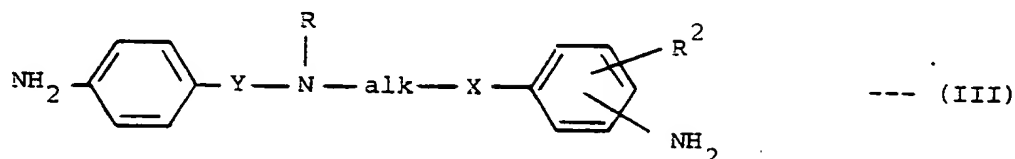
The reaction is typically carried out in a suitable organic solvent at room temperature, and optionally in the presence of a base ("acid acceptor") such as pyridine, triethylamine, sodium bicarbonate or potassium carbonate. The presence of an acid acceptor is especially useful when an alkanesulphonyl chloride or bromide is used as the acylating agent. It is preferred to use the sulphonic anhydride (R¹SO₂)₂O in methylene chloride or sulphonyl chloride R¹SO₂Cl in pyridine as the sulphonylating agent. The product (I) can then be isolated and purified by conventional techniques.

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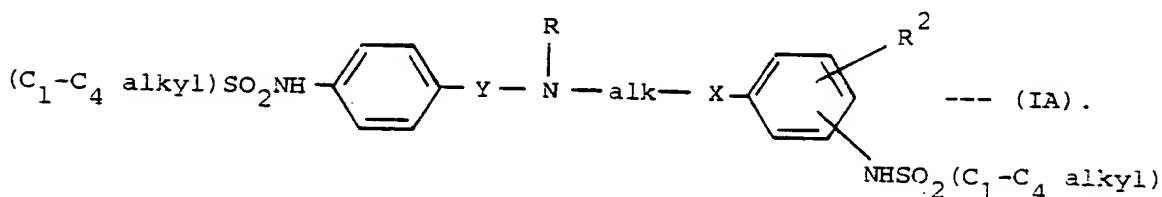
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Route II

When R^3 is $-NHSO_2(C_1-C_4 \text{ alkyl})$, then the following route, starting from an intermediate in which R^a and R^b are $-NH_2$, is particularly useful:-



$(C_1-C_4 \text{ alkyl}.SO_2)_2O$, $(C_1-C_4 \text{ alkyl}).SO_2Cl$
 or $(C_1-C_4 \text{ alkyl}).SO_2Br$ (optionally in
 the presence of an acid acceptor).



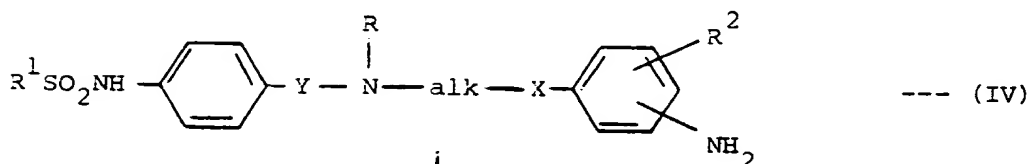
R , R^2 , X , Y and "alk" are as defined for formula (I).

The reaction can be carried out similarly to Route I, although at least 2 equivalents of the sulphonylating agent must of course be used and, in the end product (IA), each alkylsulphonamido group will be the same.

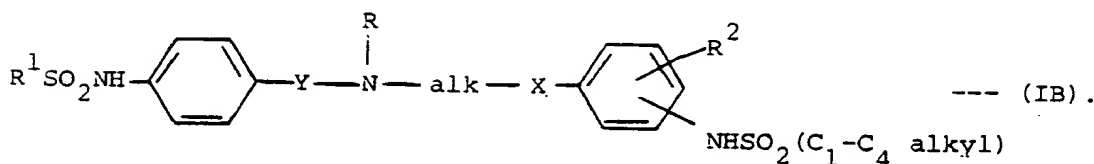
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Route III

When R^3 is $-\text{NHSO}_2(\text{C}_1-\text{C}_4 \text{ alkyl})$, then the following route, starting from a compound in which R^b is $-\text{NH}_2$, can also be used:-



$(\text{C}_1-\text{C}_4 \text{ alkyl}.\text{SO}_2)_2\text{O}$, $(\text{C}_1-\text{C}_4 \text{ alkyl}).\text{SO}_2\text{Cl}$
 or $(\text{C}_1-\text{C}_4 \text{ alkyl}).\text{SO}_2\text{Br}$ (optionally in the presence of an acid acceptor).



R , R^1 , R^2 , X , Y and "alk" are as defined for formula (I).

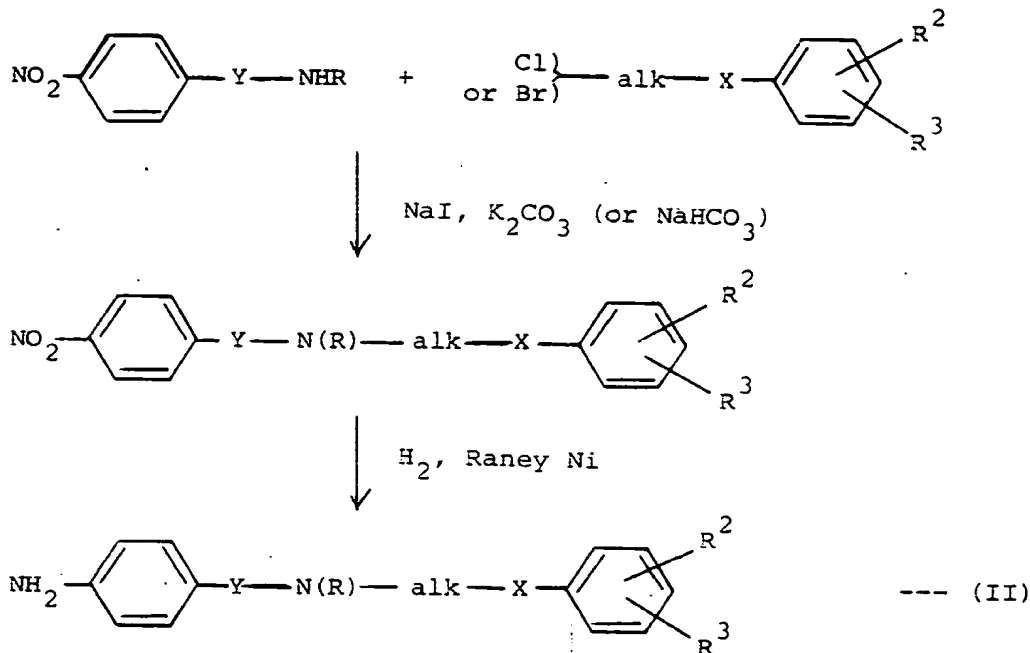
5 The reaction can again be carried out similarly to Route I. Clearly this route can be used to prepare end products in which the alkanesulphonamido substituents are different.

The novel intermediates used in Routes I to III also form a part of the invention and these have the formula (A) as previously defined with the additional proviso that either at least one of R^a and R^b is nitro, or at least one of R^a and R^b is amino.

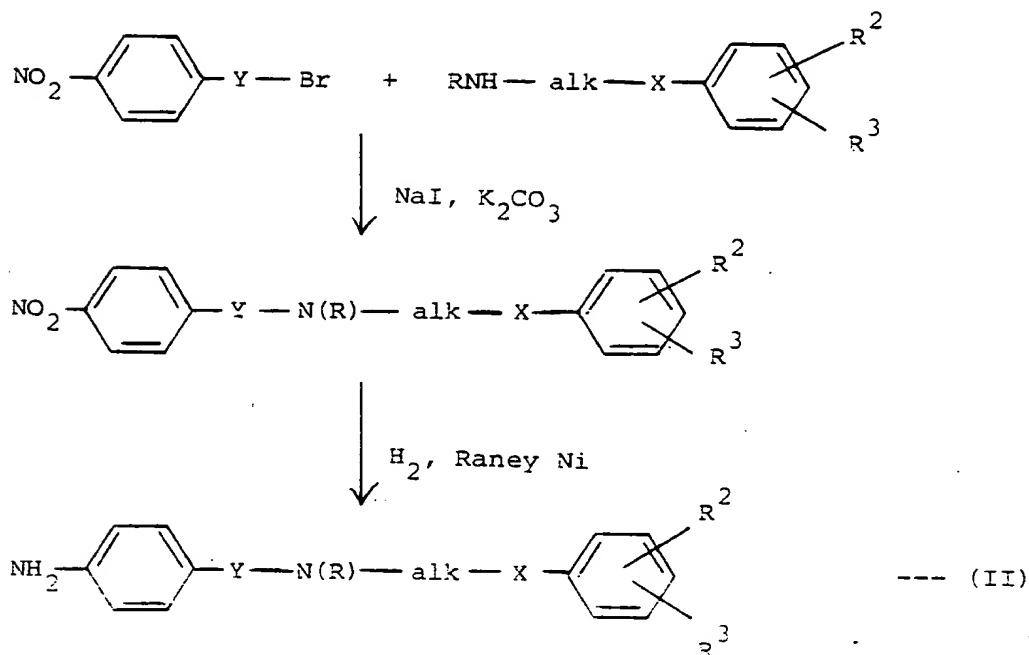
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The starting materials for the above routes are obtainable by conventional methods, e.g. as follows:

(a)



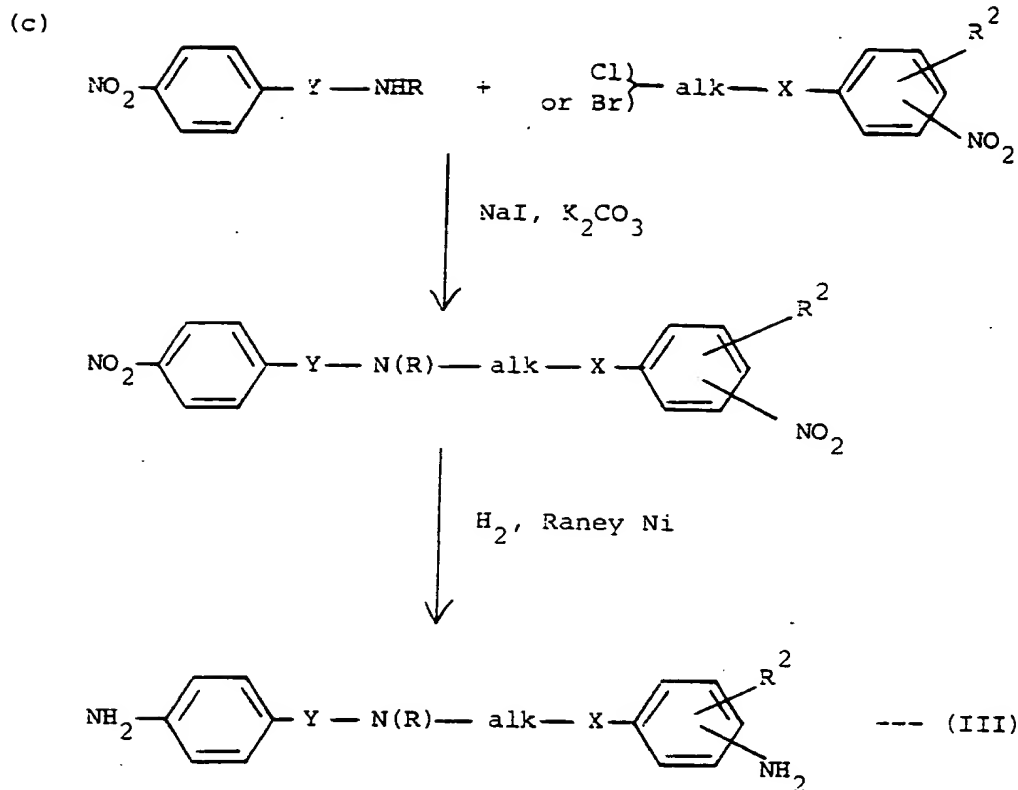
(b)



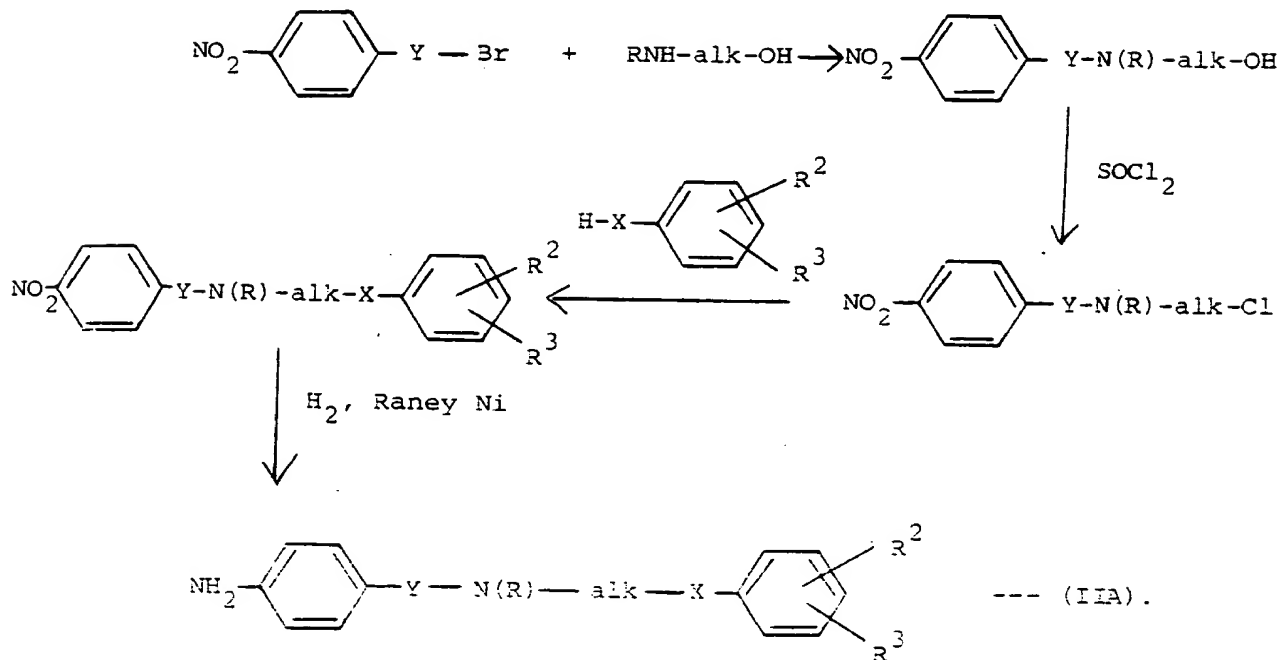
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(d) For intermediates in which X is O or S only:-



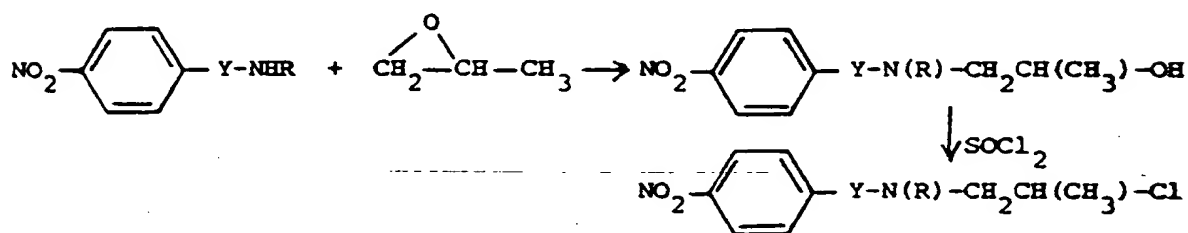
[X = O or S only.]

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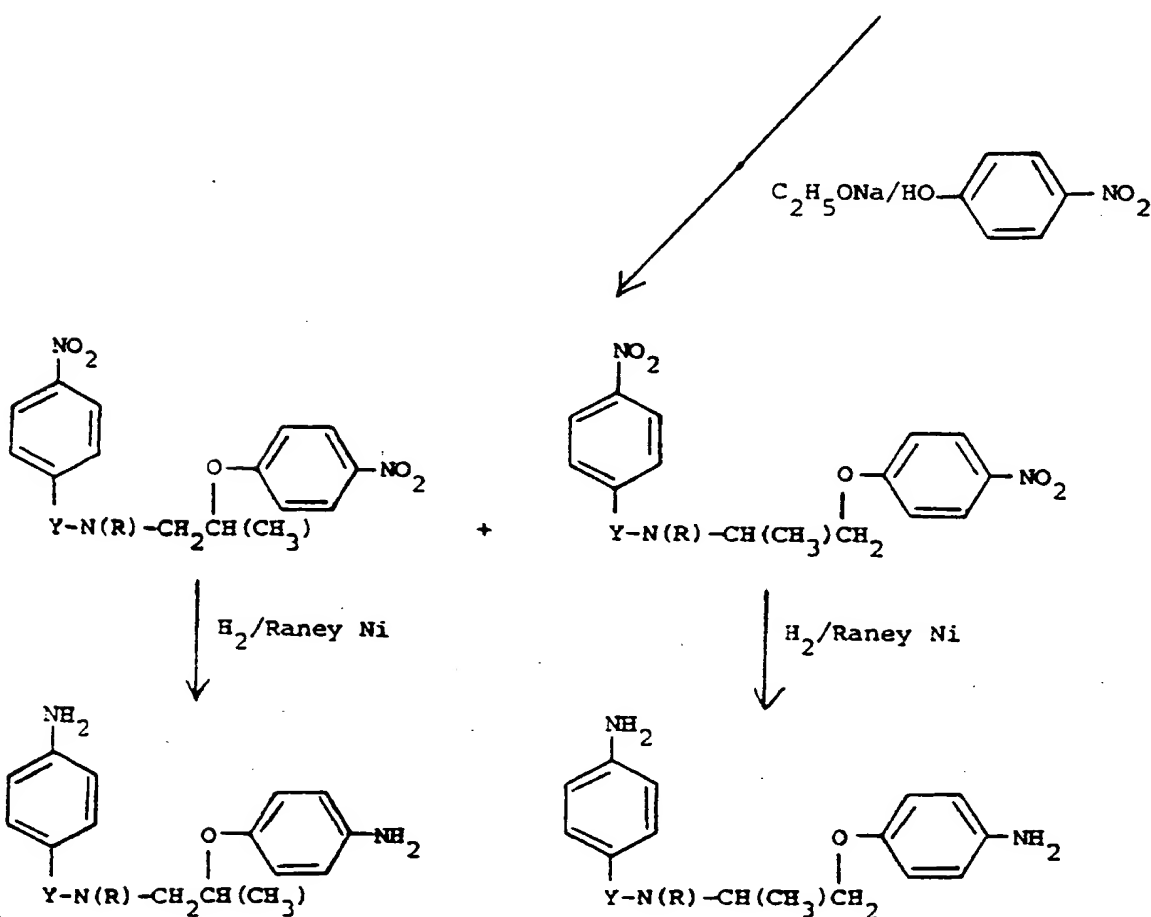
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In a modification of this route, a thiophenol or phenol in which R^3 is nitro can be used. The hydrogenation step will also reduce this nitro group to amino [as in route (c) above], thus producing an intermediate of the formula (III) in which X is S or O.

A further modification of this route, useful in preparing certain compounds of the formula (IIA) having "alk" as $-\text{CH}(\text{CH}_3)\text{CH}_2-$ or $-\text{CH}_2\text{CH}(\text{CH}_3)-$, is as follows:



T1/20X



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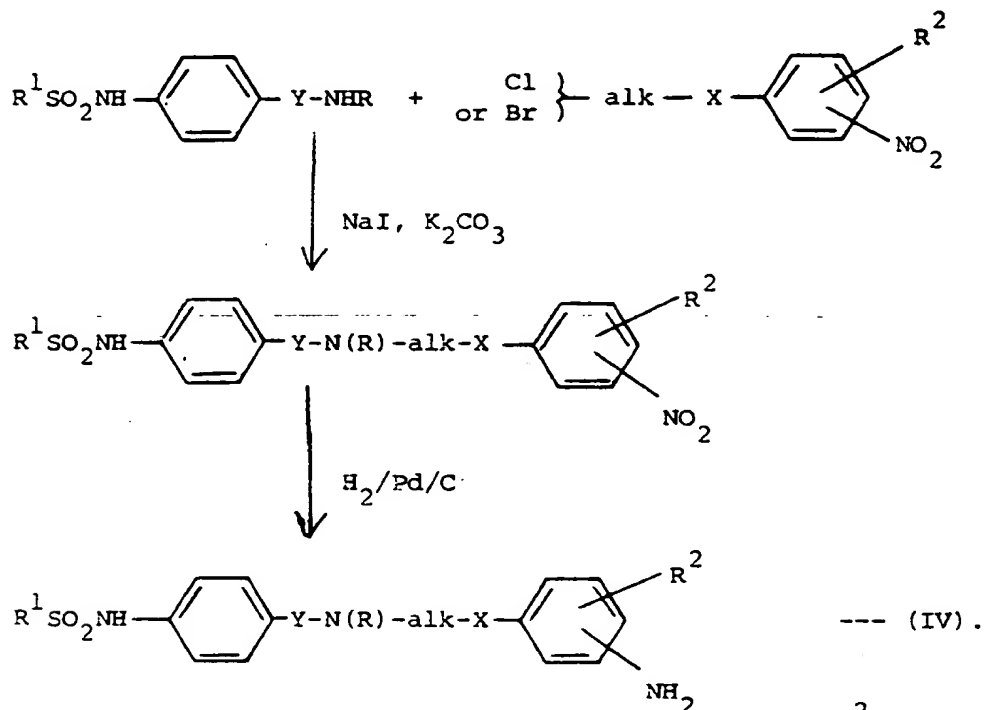
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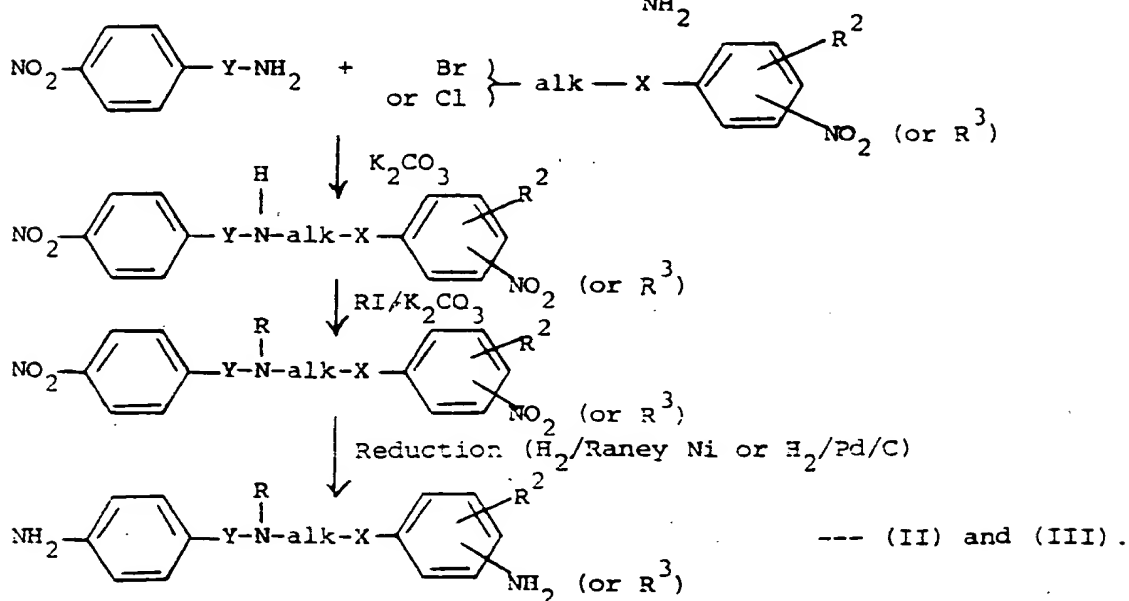
The mixture of the 2 nitro-containing compounds is believed to result from the competitive ring opening of an intermediate aziridinium cation formed in the reaction. The nitro-containing intermediates can be separated by chromatography prior to the catalytic hydrogenation step.

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(e)



(f)

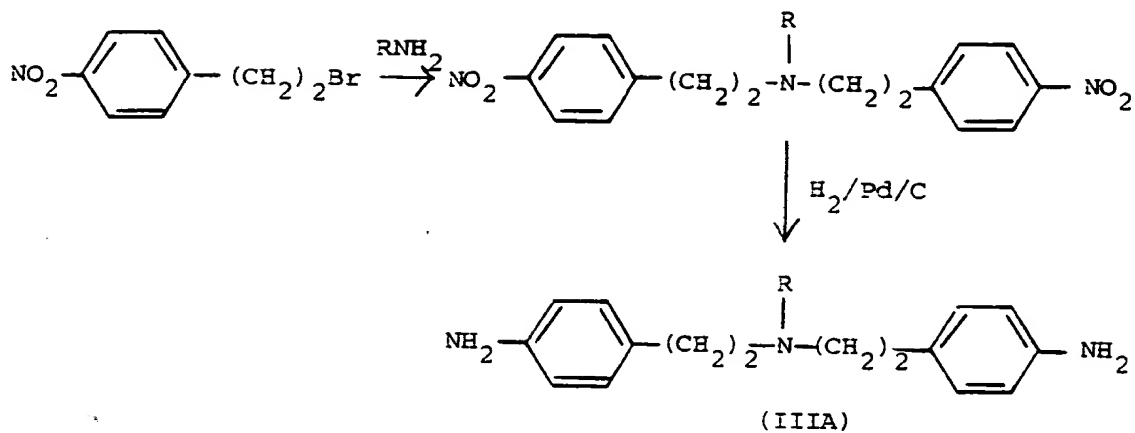


T. 130X

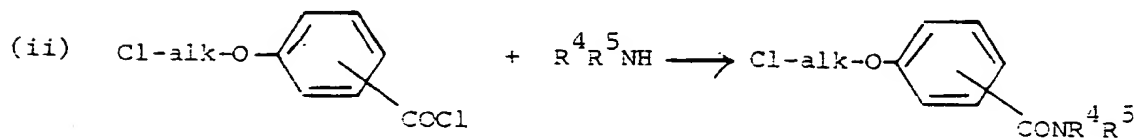
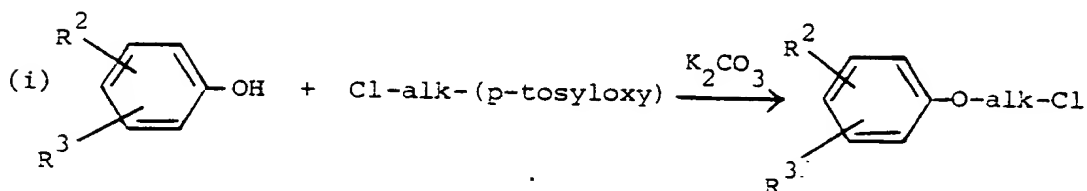
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and (g)



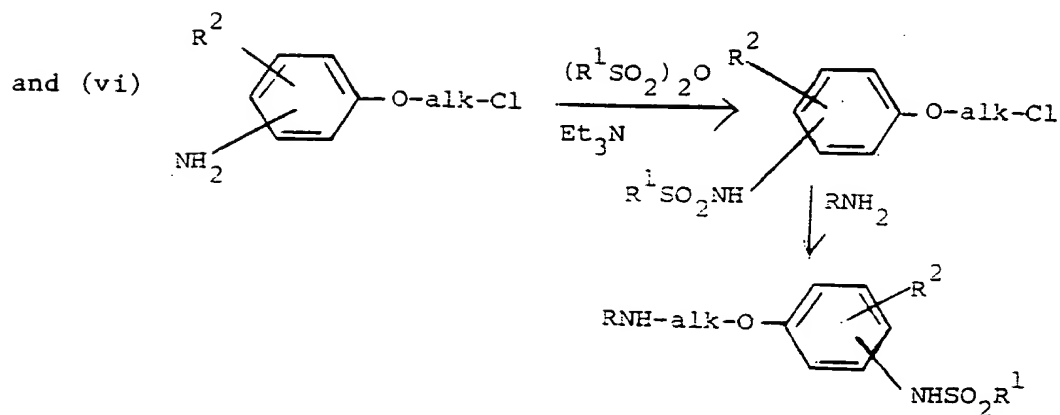
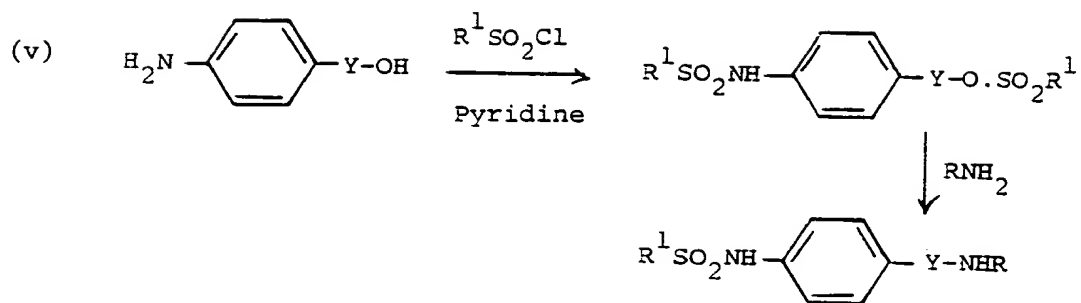
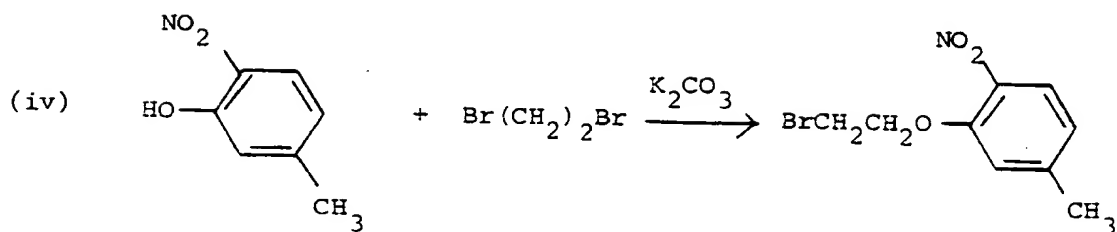
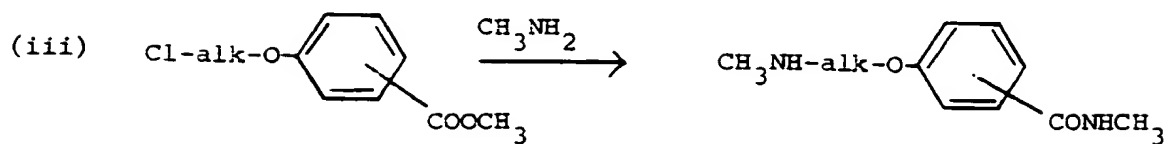
Where the starting materials used in (a) to (g) above are not known compounds, they can again be prepared by conventional techniques, e.g. as follows:



T1140x

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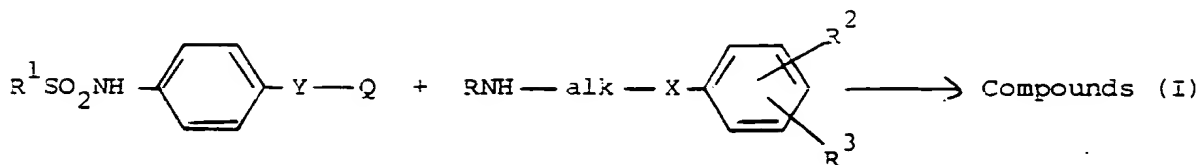
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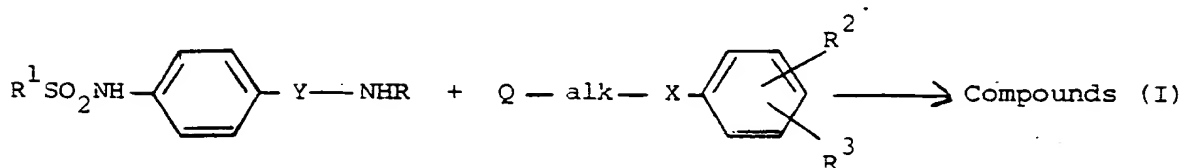
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Route IV

The compounds of the formula (I) can also be prepared as follows:-



or



In the above, R, R¹, R², R³, X, Y and alk are as defined for formula (I), and Q is a leaving group, e.g. chloro, bromo, iodo, C₁-C₄ alkanesulphonyloxy (particularly methanesulphonyloxy), benzenesulphonyloxy or toluenesulphonyloxy. The presence of an acid acceptor such as sodium bicarbonate, triethylamine or potassium carbonate is optional, but is preferred when Q is halo.

The reaction is typically carried out in an organic solvent, e.g. ethanol, at up to the reflux temperature, typically at up to about 120°C. It is preferred to carry out the reaction under reflux. The product can then be isolated and purified by conventional means.

The starting materials can again be obtained conventionally.

When the compounds of the formula (I) contain one or more optically active centres, then the invention encompasses both resolved and unresolved forms.

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The pharmaceutically acceptable salts of the compounds of the formula (I) include acid addition salts formed from acids which form non-toxic acid addition salts containing pharmaceutically acceptable anions, such as hydrochloride, hydrobromide, hydroiodide, sulphate or bisulphate, phosphate or hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, benzoate, methanesulphonate, besylate and p-toluenesulphonate salts. The compounds also form metal salts, preferred examples of which are the alkaline earth and alkali metal salts. The sodium and potassium salts are most preferred. The salts are preparable by conventional techniques.

For assessment of effects of the compounds on atrial refractoriness, guinea pig right hemiatria are mounted in a bath containing physiological salt solution, and one end is connected to a force transducer. Tissues are stimulated at 1 Hz using field electrodes. Effective refractory period (ERP) is measured by introducing premature stimuli (S_2) after every 8th basic stimulus (S_1). The S_1S_2 coupling interval is gradually increased until S_2 reproducibly elicits a propagated response. This is defined as the ERP. The concentration of compound required to increase ERP by 25% (ED_{25}) is then determined. ERP is also measured in guinea pig right papillary muscles incubated in physiological salt solution. Muscles are stimulated at one end using bipolar electrodes and the propagated electrogram is recorded at the opposite end via a unipolar surface electrode. ERP is determined as above using the extrastimulus technique. Conduction time is

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obtained from a digital storage oscilloscope by measuring the interval between the stimulus artefact and the peak of the electrogram (i.e. the time required for the impulse to travel along the length of the muscle).

3 5 Atrial and ventricular ERP's are also measured in anaesthetised or conscious dogs by the extrastimulus technique whilst the atrium or right ventricle is being paced at a constant rate.

10 The compounds of the formula (I) can be administered alone but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. They can be administered both to patients suffering from arrhythmias and also prophylactically to those likely to develop arrhythmias. For
15 example they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. They may be injected parenterally, for example, intravenously,
20 intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other solutes, for example, enough salts or glucose to make the solution isotonic.

25 For administration to man in the curative or prophylactic treatment of cardiac conditions such as ventricular and supraventricular arrhythmias, including atrial and ventricular fibrillation, it is expected that oral dosages of the compounds of the formula (I) will be in the range from 1 to 75 mg daily, taken

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in up to 4 divided doses per day, for an average adult patient
(70 kg). Dosages for intravenous administration would be expected
to be within the range 0.5 to 10mg per single dose as required. A
severe cardiac arrhythmia is preferably treated by the i.v. route
in order to effect a rapid conversion to the normal rhythm. Thus
for a typical adult patient individual tablets or capsules might
for example contain 1 to 25mg of active compound, in a suitable
pharmaceutically acceptable vehicle or carrier. Variations may
occur depending on the weight and condition of the subject being
treated as will be known to medical practitioners.

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The following Examples, in which all temperatures are in °C, illustrate the preparation of the compounds of the formula (I).

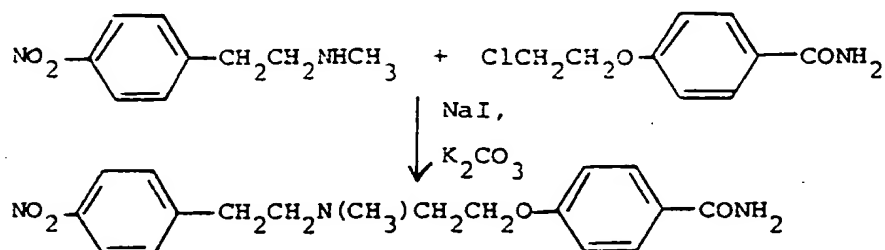
In these Examples, 3 atmospheres is equivalent to 3.04×10^5 Pa, and 50 p.s.i. to 3.45×10^5 Pa.

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EXAMPLE 1

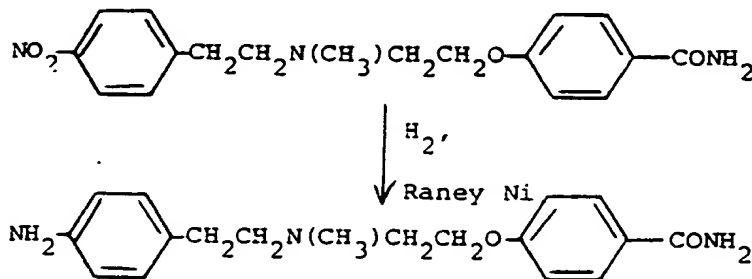
(A) 4-(2-[N-Methyl-N-(4-nitrophenethyl)amino]ethoxy)benzamide



To a solution of N-methyl-4-nitrophenethylamine (1.8 g) [J.O.C., (1956), 21, 45] and 4-(2-chloroethoxy)benzamide (see Preparation 12) in acetonitrile (100 ml) was added potassium carbonate (3.0 g) and sodium iodide (1.5 g) and the suspension stirred at reflux for 72 hours. After evaporation, a 2N aqueous sodium bicarbonate solution was added to the residual oily solid and then extracted three times with methylene chloride. The combined organic layers were washed with a saturated aqueous brine solution, dried over magnesium sulphate, filtered and evaporated to give a yellow oil. Trituration of the oil with diisopropyl ether gave 2.3 g of a yellow solid which was crystallised from toluene to give the title compound (1.4 g), m.p. 116-118°, which was used directly without further purification.

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(B) 4- $\{$ 2-[N-(4-Aminophenethyl)-N-methylamino]ethoxy $\}$ benzamide



A solution of 4- $\{$ 2-[N-methyl-N-(4-nitrophenethyl)amino]-ethoxy $\}$ benzamide (1.4 g) in ethanol (100 ml) was stirred for 16 hours at room temperature under three atmospheres of hydrogen in the presence of Raney nickel ("Nicat 102", Trade Mark). The reaction mixture was filtered and evaporated to dryness to give a yellow solid (1.2 g) which crystallised from ethyl acetate to give the title compound, (1.1 g), m.p. 110-112°.

Analysis %:-

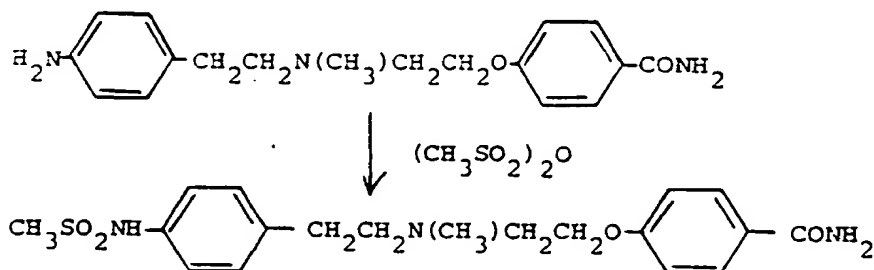
Found:

C, 69.1; H, 7.3; N, 13.05;

Calculated for C₁₈H₂₃N₃O₂:

C, 69.0; H, 7.4; N, 13.4.

(C) 4- Σ 2-[N-Methyl-N-(4-methanesulphonamidophenethyl)amino]-ethoxy} benzamide



A solution of 4- Σ 2-[N-(4-aminophenethyl)-N-methylamino]-ethoxy} benzamide (1.0 g) and methanesulphonic anhydride in dry methylene chloride (50 ml) was stirred at room temperature for 16 hours. After evaporation a 2N aqueous sodium bicarbonate solution was added to the residue followed by extraction three times with methylene chloride. The combined organic layers were dried over magnesium sulphate, filtered and evaporated to give a light brown solid. Crystallisation from toluene/ethyl acetate gave the title compound (0.31 g), m.p. 147°.

Analysis %:-

Found:

C, 58.35; H, 6.7; N, 10.45;

Calculated for $C_{19}H_{25}N_3O_4S$:

C, 58.3; H, 6.4; N, 10.7.

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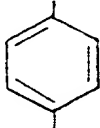
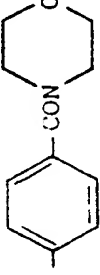
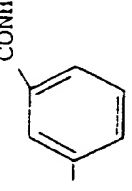
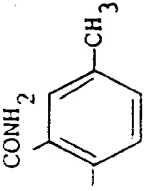
EXAMPLES 2 TO 5

The following compounds were prepared similarly to Example 1 parts (A) to (C) from appropriate starting materials. In Examples 3 and 5, the products were characterised as hydrochloride salts by adding ethyl acetate to the solid resulting from the second evaporation step in part (C), followed by treatment with ethereal hydrogen chloride, filtering off the resulting hydrochloride salt, and recrystallising it from ethyl acetate/methanol.

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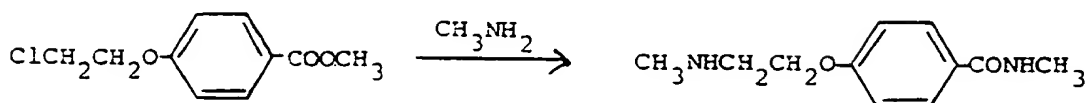


Example No.	Ar	Form Isolated	Recrystallization Solvent	m.p. (°C)	Analysis % (Theoretical in Brackets) C H N
2		Free base	Diisopropyl ether/ ethyl acetate	97-98	61.7 7.25 9.1 (61.7 7.4 9.4)
3		Hydrochloride hemihydrate	Ethyl acetate/ methanol	198-201	55.0 6.3 8.0 (54.5 6.6 8.3)
4		Free base	Ethyl acetate	104-106	57.8 6.4 10.6 (58.3 6.4 10.7)
5		Hydrochloride	Ethyl acetate/ methanol	124-126	54.7 6.7 9.1 (54.3 6.4 9.5)

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EXAMPLE 6

(A) N-Methyl-4-(2-methylaminoethoxy)benzamide



To a 33% solution of methylamine in industrial methylated spirits (50 ml) was added methyl 4-(2-chloroethoxy)benzoate (4.3 g) (see Preparation 11) and the mixture was stirred while heating at 100° in a 130 ml sealed pressure vessel for 16 hours. After evaporation to dryness, the resultant solid was added to 10 ml of 2N aqueous sodium hydroxide solution and extracted three times with methylene chloride. The combined organic layers were dried over anhydrous magnesium sulphate, filtered and evaporated to give a colourless solid. Crystallisation from isopropanol gave the title compound, (2.1 g), m.p. 95-96°.

Analysis %:-

Found:

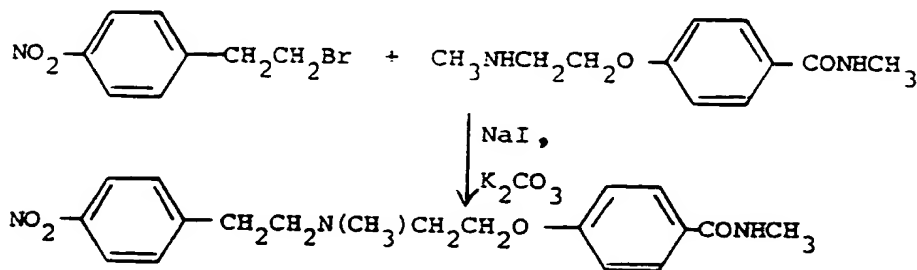
C, 63.7; H, 7.6; N, 13.4;

Calculated for $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_2$:

C, 63.4; H, 7.7; N, 13.45.

EXPRESS MAIL NO. 20304533

(B) N-Methyl-4-[2-(N'-methyl-N'-(4-nitrophenethyl)amino)ethoxy]-benzamide



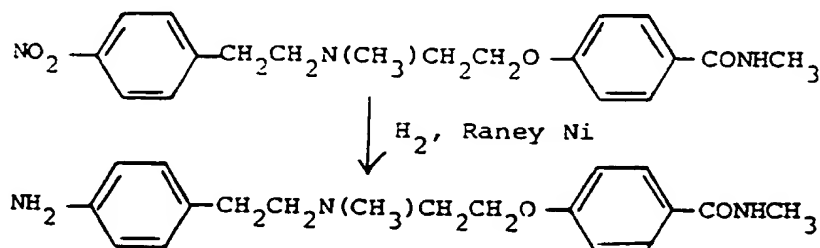
To a solution of N-methyl-4-(2-methylaminoethoxy)benzamide and 4-nitrophenethyl bromide in acetonitrile (100 ml) was added potassium carbonate (3.0 g) and sodium iodide (1.5 g) and the suspension was stirred at reflux for 72 hours. After evaporation, a 2N aqueous sodium hydroxide solution was added followed by extraction three times with methylene chloride. The combined organic layers were washed with a saturated aqueous brine solution, dried over magnesium sulphate, filtered and evaporated to give a yellow oil. Trituration of the oil with diisopropyl ether gave the title compound as a yellow solid, (2.4 g), which was used without further purification.

N.m.r. (CDCl_3), ppm, δ = 7.9 (d, 2H); 7.52 (d, 2H); 7.12 (d, 2H); 5.63 (d, 2H); 3.9 (t, 2H); 2.8 (m, 9H); 2.28 (s, 3H).

27

EXPRESS MAIL NO. 15 20204523

(C) N-Methyl-4- ξ 2-[N'-(4-aminophenethyl)-N'-methylamino]ethoxy ζ -benzamide



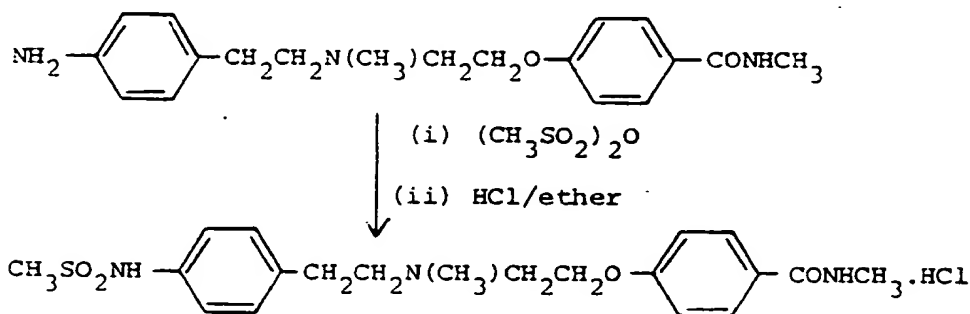
A solution of N-methyl-4- ξ 2-[N'-methyl-N'-(4-nitro-phenethyl)amino]ethoxy ζ benzamide (2.3 g) in ethanol (100 ml) was stirred for 16 hours at room temperature under three atmospheres of hydrogen in the presence of Raney nickel ("Nicat 102" - Trade Mark). The reaction mixture was filtered and evaporated to dryness to give a yellow oil (2.1 g). Chromatography on silica ("Kieselgel 60" - Trade Mark) eluting with ethyl acetate gave the title compound as a colourless oil, (1.7 g), which was used directly without further purification.

N.m.r. (CDCl₃) ppm, δ = 7.72 (d, 2H); 7.0 (d, 2H); 6.92 (d, 2H); 6.62 (d, 2H); 3.0 (d, 3H); 2.88 (t, 2H); 2.7 (s, 4H); 2.42 (s, 3H).

28

EXPRESS MAIL NO. 16 30204523

(D) N-Methyl-4- ξ 2-[N'-(4-methanesulphonamidophenethyl)-N'-methylamino]ethoxy ξ benzamide hydrochloride



A solution of N-methyl-4- ξ 2-[N'-(4-aminophenethyl)-N'-methylamino]ethoxy ξ benzamide (1.6 g) and methanesulphonic anhydride (0.87 g) in dry methylene chloride (50 ml) was stirred at room temperature overnight. After evaporation, the resultant oily solid was treated with a 2N aqueous sodium bicarbonate solution and extracted three times with methylene chloride. The combined organic layers were washed with a saturated aqueous brine solution, dried over magnesium sulphate, filtered and evaporated. Chromatography on silica ["Kieselgel 60" - Trade Mark] eluting with ethyl acetate gave a colourless oil (0.52 g). The oil was dissolved in ethyl acetate and an ethereal solution of hydrogen chloride was added until precipitation was complete. The colourless solid was filtered off and crystallised from ethyl acetate/methanol to give the title compound, (0.2 g), m.p. 160°.

29

EXPRESS MAIL NO. 630204523

Analysis %:-

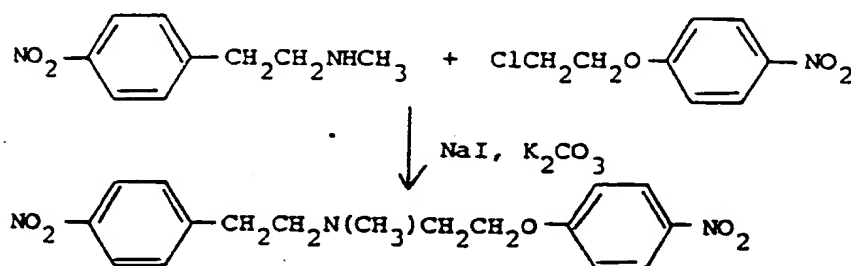
Found:

C, 54.2; H, 6.6; N, 9.25;

Calculated for $C_{20}H_{27}N_3O_4S.HCl$: C, 54.35; H, 6.4; N, 9.5.

EXAMPLE 7

(A) 1-(4-Nitrophenoxy)-2-[N-methyl-N-(4-nitrophenethyl)amino]-ethane



To a solution of N-methyl-4-nitrophenethylamine (1.5 g) (J.O.C., [1956], 21, 45) and 2-[4-nitrophenoxy]ethyl chloride (1.55 g) (C.A., [1955], 49, 3163e) in acetonitrile (50 ml) was added potassium carbonate (1.25 g) and sodium iodide (1.2 g) and the suspension was stirred at reflux for 72 hours. After evaporation to dryness, the residual oily solid was partitioned between a 2N aqueous sodium bicarbonate solution and ethyl acetate. After two further extractions with ethyl acetate, the organic portions were combined, washed with a saturated aqueous

EXPRESS MAIL NO. B 20207523

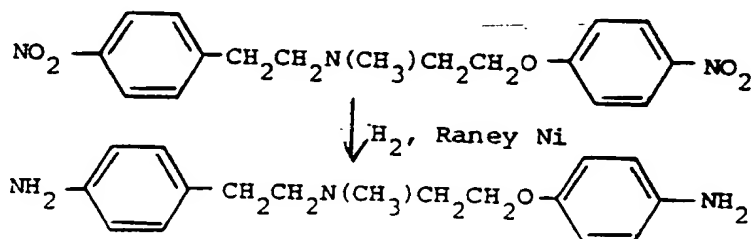
brine solution, dried over magnesium sulphate, filtered and evaporated. The resultant orange solid (2.7 g) was crystallised from ethanol to give the title compound, (1.9 g), m.p. 74°.

Analysis %:

Found: C, 58.75; H, 5.4; N, 12.15;

Calculated for $C_{17}H_{19}N_3O_4$: C, 59.1; H, 5.5; N, 12.2.

(B) 1-(4-Aminophenoxy)-2-[N-(4-aminophenethyl)-N-methylamino]-ethane



A solution of 1-(4-nitrophenoxy)-2-[N-methyl-N-(4-nitrophenethyl)amino]ethane (1.5 g) in ethanol (100 ml) was stirred for 16 hours at room temperature under three atmospheres of hydrogen in the presence of Raney nickel ("Nicat 102" - Trade Mark). The reaction mixture was filtered and evaporated to dryness. The residual oil was re-dissolved in ether, filtered and evaporated to give a yellow solid (1.1 g), which was crystallised from ethyl acetate/60-80° petroleum ether to give the title compound, (0.9 g), m.p. 73-74°.

EXPRESS MAIL NO. B 30704523

Analysis %:-

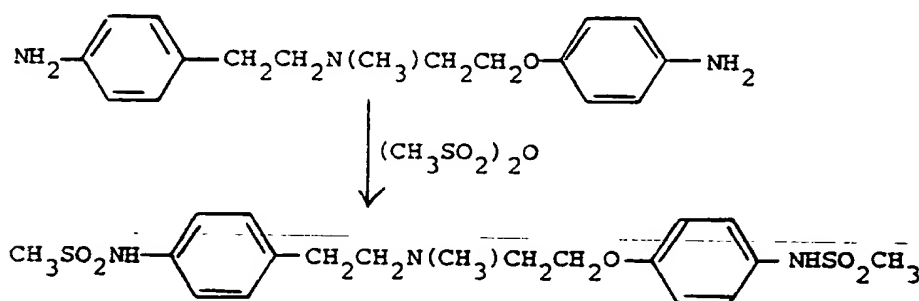
Found:

C, 71.3; H, 8.1; N, 14.7;

Calculated for $C_{17}H_{23}N_3O$:

C, 71.55; H, 8.1; N, 14.7.

(C) 1-(4-Methanesulphonamidophenoxy)-2-[N-(4-methanesulphonamido-phenethyl)-N-methylamino]ethane



A solution of 1-(4-aminophenoxy)-2-[N-(4-aminophenethyl)-N-methylamino]ethane (0.75 g) and methanesulphonic anhydride (1.0 g) in dry methylene chloride (50 ml) was stirred at room temperature overnight. After evaporation, the resultant oil was partitioned between a 2N aqueous sodium bicarbonate solution and ethyl acetate. After two further extractions with ethyl acetate, the organic portions were combined, dried over magnesium sulphate, filtered and evaporated. The resultant colourless solid (1.2 g) was crystallised from ethyl acetate/methanol to give the title compound, (0.6 g), m.p. 147-149°.

32

EXPRESS MAIL NO. B-2020523

Analysis %:-

Found:

C, 52.1; H, 6.25; N, 9.45;

Calculated for $C_{19}H_{27}N_3O_5S_2$:

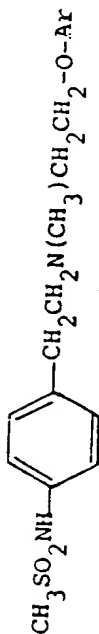
C, 51.9; H, 6.15; N, 9.4.

EXAMPLES 8 to 14

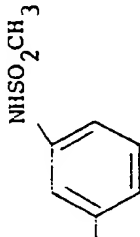
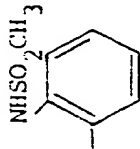
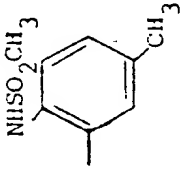
The following compounds were prepared similarly to the procedure of the previous Example parts (A) to (C), starting from corresponding starting materials except that in part (A) 2-(nitrophenoxy)ethyl bromides rather than chlorides were used, and were isolated in the forms indicated. The hydrochloride salts were prepared by dissolving the residue from the last evaporation step in ethyl acetate, adding ethereal hydrogen chloride, filtering off the resultant precipitate of the hydrochloride salt, followed by recrystallisation from the stated solvent.

EXPRESS MAIL NO. B20209533

T, 340X



34

Example No.	Ar	Form Isolated	Recrystallization Solvent	m.p. (°C)	Analysis % (Theoretical in Brackets) C H N
8		Free base	60-80° Petroleum ether/ethyl acetate	113-4	51.9 6.45 9.0 (51.7 6.2 9.5)
9		Hydrochloride	Ethyl acetate/ methanol	178-80	47.7 6.0 8.6 (47.7 5.9 8.8)
10		Hydrochloride hydrate	Ethyl acetate/ methanol	185 (foams)	47.0 6.1 8.0 (47.1 6.3 8.2)

EXPRESS MAIL NO. 50204523

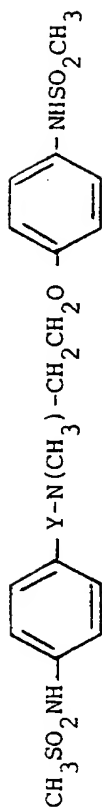


Example No.	"Alk"	Form Isolated	Recrystallization Solvent	m.p. (°C)	Analysis % (Theoretical in Brackets) C H N
11	$-(\text{CH}_2)_3-$	Hydrochloride	EtOAc/MeOH	125°*	(48.8 6.2 8.5) 48.5 6.4 8.2
12	$-(\text{CH}_2)_4-$	Hydrochloride Hemihydrate	EtOAc/MeOH	>90°*	(49.0 6.5 8.2) 49.2 6.6 7.7

* Foams

The starting materials 4-(3-bromopropoxy)nitrobenzene and 4-(4-bromobutoxy)nitrobenzene are described, respectively, in J.A.C.S. (1951), 73, 3159 and C.A., 59, 9883.

EXPRESS MAIL NO. 20204523



Example No.	Y	Form Isolated	Recrystallization Solvent	m.p. (°C)	Analysis % (Theoretical in Brackets) C H N
13	$\begin{array}{c} \text{CH}_3 \\ \\ -\text{CH}_2\text{CH}- \end{array}$	Hydrochloride Hemihydrate	EtOAc/MeOH	> 106° (hygroscopic)	47.8 6.4 8.2 (47.9 6.2 8.4)
14	$\begin{array}{c} \text{CH}_3 \\ \\ -\text{CHCH}_2- \end{array}$	Hydrochloride	EtOAc/MeOH	> 98° (hygroscopic)	49.0 6.2 8.2 (48.8 6.15 8.5)

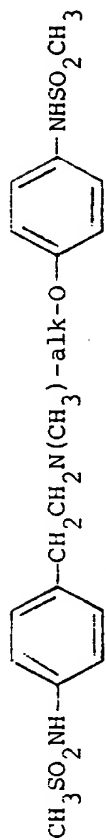
The starting materials N-methyl-1-(4-nitrophenyl)-2-propylamine and N-methyl-2-(4-nitrophenyl)-1-propylamine are described in J.A.C.S., (1946), 68, 1153.

EXPRESS MAIL NO. 320 45 23

EXAMPLES 15 and 16

CL
P
5 The following compounds were prepared similarly to the procedure of Example 7 parts (B) and (C) using corresponding starting materials [see Preparation 6 parts (C) and (D)] except that in part (C) methanesulphonyl chloride in pyridine was used rather than methanesulphonic anhydride in methylene chloride. In Example 16, the hydrochloride salt was obtained as described in the relevant description relating to Examples 8 to 14.

EXPRESS MAIL NO. D 20204523



Example No.	Alk	Form Isolated	Recrystallization Solvent	m.p. (°C)	Analysis % (Theoretical in Brackets) C H N
15	$\begin{array}{c} \text{CH}_3 \\ \\ -\text{CH}-\text{CH}_2- \end{array}$	Free base	Hexane/EtOAc	120°	$\begin{array}{ccc} 52.8 & 6.5 & 8.9 \\ (52.7) & (6.4) & (9.2) \end{array}$
16	$\begin{array}{c} \text{CH}_3 \\ \\ -\text{CH}_2-\text{CH}- \end{array}$	Hydrochloride Hemihydrate	EtOAc/MeOH	> 100° (hygroscopic)	$\begin{array}{ccc} 48.1 & 6.3 & 8.2 \\ (47.9) & (6.2) & (8.4) \end{array}$

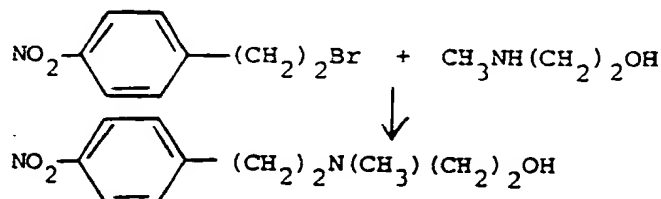
T₁350X

38

EXPRESS MAIL NO. 20204523

EXAMPLE 17

(A) 2-[N-Methyl-N-(4-nitrophenethyl)amino]ethanol

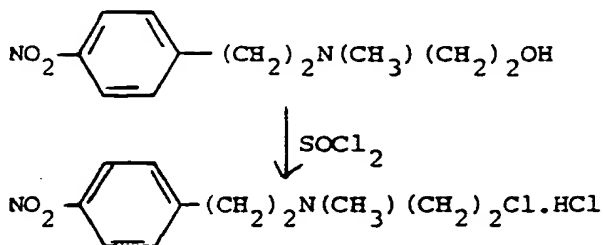


A mixture of 4-nitrophenethyl bromide (11.5 g) and N-methylethanolamine (8.25 g) in xylene (100 ml) was stirred at reflux for 16 hours. After evaporation, the residue was partitioned between 5% aqueous sodium bicarbonate and methylene chloride. The organic liquors were washed with saturated aqueous brine, dried (MgSO₄), filtered and evaporated to give an orange oil (10.1 g). Chromatography on silica ("Kieselgel 60" - Trade Mark) eluting with ethyl acetate followed by collection and evaporation of suitable fractions gave the title compound as a yellow oil, (7.5 g).

N.m.r. (CDCl₃) ppm, δ = 8.05 (d, 2H); 7.2 (d, 2H); 3.52 (t, 2H); 2.61 (m, 6H); 2.3 (s, 3H).

EXPRESS MAIL NO. B 30304520

(B) 2-[N-Methyl-N-(4-nitrophenethyl)amino]ethyl chloride
hydrochloride



To a solution of 2-[N-methyl-N-(4-nitrophenethyl)amino]-ethanol (8.0 g) in dry methylene chloride (75 ml) was added dropwise thionyl chloride (3 ml) with stirring at 0°C. The mixture was allowed to warm to ambient temperature and stirred for 16 hours. The resultant solid was filtered, washed with dry ether and dried to give a colourless product (7.1 g). Crystallisation from ethyl acetate/methanol gave the title compound, 6.0 g, m.p. 168-9°.

Analysis %:-

Found:

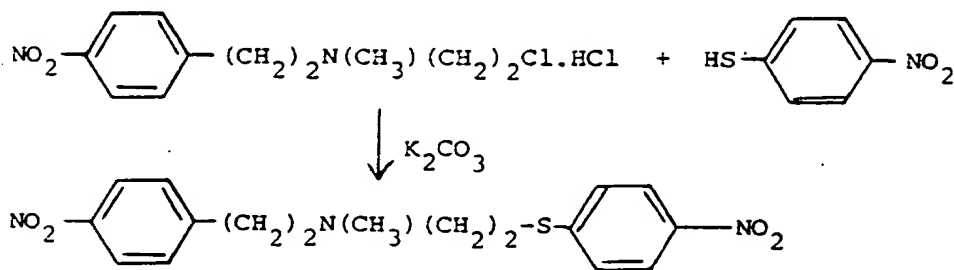
C, 46.8; H, 5.8; N, 9.85;

Calculated for $\text{C}_{11}\text{H}_{15}\text{ClN}_2\text{O}_2 \cdot \text{HCl}$: C, 47.3; H, 5.8; N, 10.0.

40

EXPRESS MAIL NO. 75 30204523

(C) 2-[N-Methyl-N-(4-nitrophenethyl)amino]-1-(4-nitrophenylthio)ethane



2-[N-Methyl-N-(4-nitrophenethyl)amino]ethyl chloride hydrochloride (3.0 g), 4-nitrothiophenol (1.7 g) and potassium carbonate (4.0 g) in acetonitrile (100 ml) were stirred at reflux for 16 hours. After evaporation, the residue was partitioned between water and ethyl acetate. The organic liquors were washed with saturated aqueous brine, dried (MgSO₄), filtered and evaporated to give an orange oil (3.6 g). Chromatography on silica ("Kieselgel 60" - Trade Mark) eluting with ethyl acetate followed by collection of suitable fractions gave on evaporation the title compound as a yellow solid, (3.05 g), m.p. 56-7°.

Analysis %:-

Found:

C, 56.8; H, 5.3; N, 11.7;

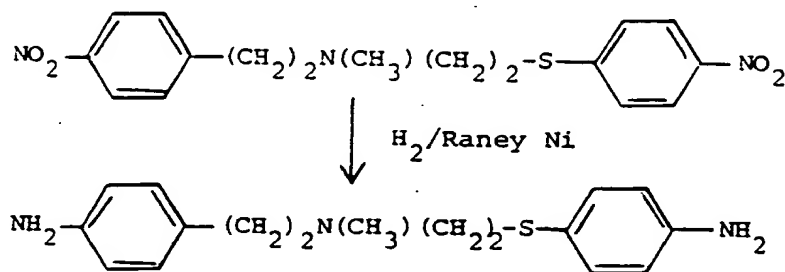
Calculated for C₁₇H₁₉N₃O₄S:

C, 56.5; H, 5.3; N, 11.6.

41

CL

(D) 1-(4-Aminophenylthio)-2-[N-(4-aminophenethyl)-N-methyl-amino]ethane



T₁ 420X

P

The title compound was prepared by the hydrogenation of 2-[N-methyl-N-(4-nitrophenethyl)amino]-1-(4-nitrophenylthio)-ethane over Raney nickel according to the procedure of Example 7(B).

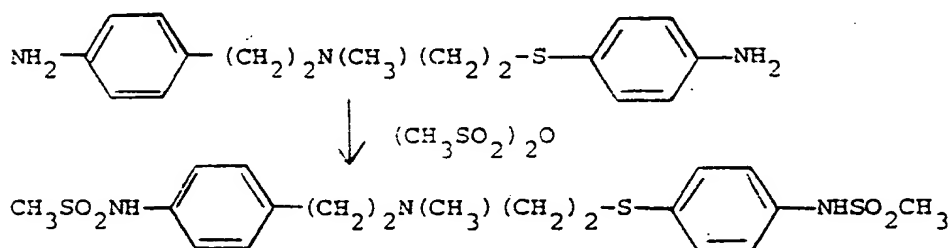
P 67

N.m.r. (CDCl₃) ppm, δ = 7.25 (d, 2H); 6.98 (d, 2H); 6.60 (m, 4H); 2.92 (t, 2H); 2.60 (m, 6H); 2.32 (s, 3H).

CL

10

(E) 1-(4-Methanesulphonamidophenylthio)-2-[N-(4-methanesulphonamidophenethyl)-N-methylamino]ethane



T₁ 421X

42

EXPRESS MAIL NO. B 2020523

P 14

The title compound, m.p. 160-3°, was prepared by the mesylation of the product of part (D) above using methanesulphonic anhydride according to the procedure of Example 7(C).

f {
H
5
Analysis %:-
1

Found:

C,49.5; H,6.1; N,8.6;

Calculated for $C_{19}H_{27}N_3O_4S_3$:

C,49.9; H,5.95; N,9.2.

EXAMPLE 18

P

The following compound was prepared similarly to the procedure of the previous Example parts (A) to (E), starting from corresponding starting materials, with the exception that the reductive step (D) was performed with $SnCl_2$ in hydrochloric acid, and that the mesylation step (E) was performed using methanesulphonyl chloride in pyridine.

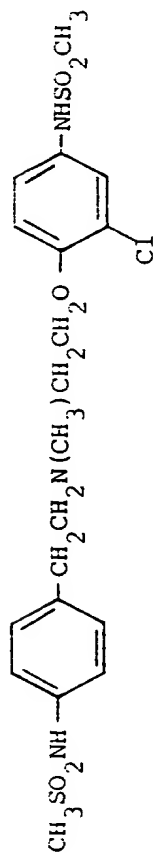
H 10

The starting material 2-chloro-4-nitrophenol is described in C.A., 34, 5574 (1940).

43

EXPRESS MAIL NO. B 20209533

T₁ 440X



Example No.	Form Isolated	Recrystallization Solvent	m.p. (°C)	Analysis % (Theoretical in brackets) C. H N		
18	Free base	Diethyl ether	141-143	47.9	5.5	8.8
				(47.8	5.6	8.5)

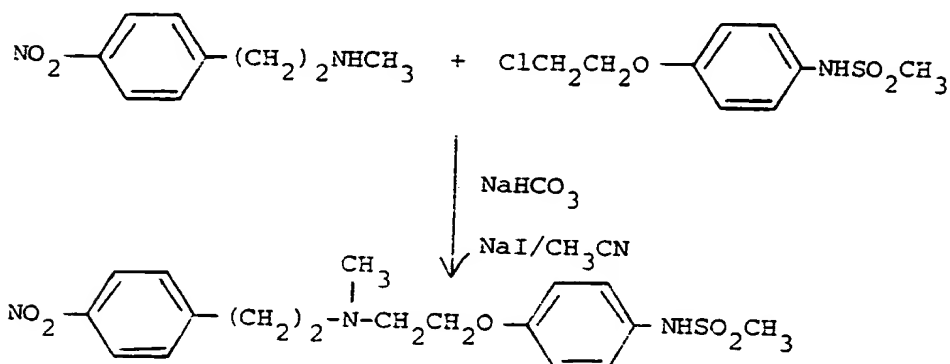
44

EXPRESS MAIL NO. B 2020 4523

CL
CL

EXAMPLE 19

(A) 1-(4-Methanesulphonamidophenoxy)-2-[N-methyl-N-(4-nitrophenethyl)amino]ethane



T₁ 430X
P

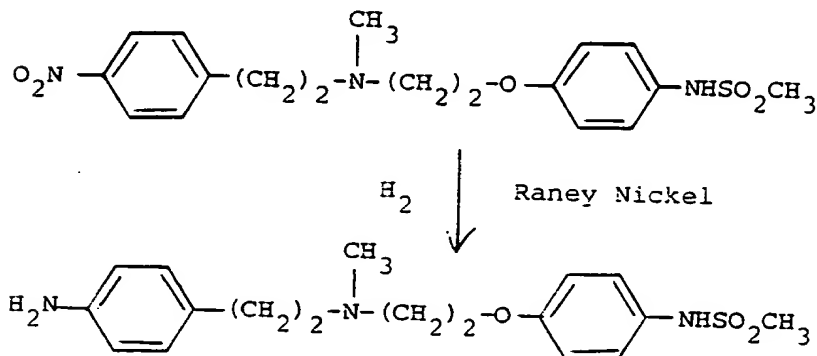
5 A suspension of N-methyl-4-nitrophenethylamine (1.1 g),
2-(4-methanesulphonamidophenoxy)ethyl chloride (1.5 g), sodium
bicarbonate (0.5 g) and sodium iodide (0.9 g) in acetonitrile (100
ml) was stirred at reflux for 4 days. On evaporation to dryness
the resultant oil was partitioned between 2N aqueous sodium
bicarbonate solution and methylene chloride. After two further
10 extractions with methylene chloride, the organic portions were
combined, washed with saturated brine solution, dried over
anhydrous magnesium sulphate, filtered and evaporated to dryness.
The resultant brown oil was chromatographed on silica ("Kieselgel
60" - Trade Mark) eluting with ethyl acetate followed by
15 collection and evaporation of suitable fractions to give the title
compound as a yellow solid, (0.9 g).

PH67

N.m.r. (CDCl₃), δ = 2.45 (s, 3H); 2.86 (m, 6H); 3.0 (s, 3H); 4.2
(t, 3H); 6.86 (d, 2H); 7.22 (d, 2H); 7.4 (d, 2H); 8.15 (d, 2H).

43

(B) 1-(4-Methanesulphonamidophenoxy)-2-[N-methyl-N-(4-amino-phenethyl)amino]ethane



A solution of 1-(4-methanesulphonamidophenoxy)-2-[N-methyl-N-(4-nitrophenethyl)amino]ethane (0.9 g) in ethanol (100 ml) was stirred for 16 hours at room temperature under three atmospheres of hydrogen in the presence of Raney Nickel ("Nicat 102" - Trade Mark). The reaction mixture was filtered and evaporated to dryness. The resultant solid was crystallised from toluene to give the title compound as yellow crystals, (0.6 g), m.p. 155-157°.

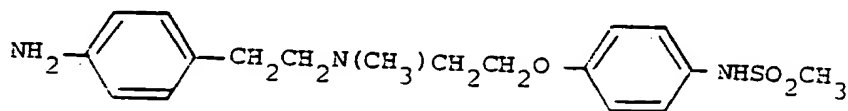
Analysis %:-

Found: C, 59.9; H, 7.1; N, 11.2;

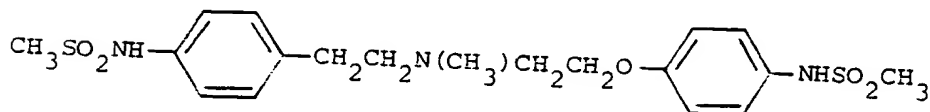
Calculated for C₁₈H₂₅N₃O₃S: C, 59.5; H, 7.0; N, 11.6.

EXPRESS MAIL NO. B 30304523

(C) 1-(4-Methanesulphonamidophenoxy)-2-[N-4-methanesulphonamido-phenethyl)-N-methylamino]ethane



CH₃SO₂Cl/Pyridine



To a solution of 1-(4-methanesulphonamidophenoxy)-2-[N-methyl-N-(4-aminophenethyl)amino]ethane (0.15 g) in dry pyridine (3 ml) was added dropwise methanesulphonyl chloride (35.4 μl) and the mixture was stirred at room temperature overnight. After evaporation, the resultant oil was partitioned between 2N aqueous sodium bicarbonate solution and methylene chloride. After two further extractions with methylene chloride, the organic portions were combined, dried over anhydrous magnesium sulphate, filtered and evaporated. The resultant colourless solid (0.135 g) was crystallised from hexane/ethyl acetate to give the title compound (0.1 g), m.p. 151-152°, confirmed spectroscopically to be identical to the product of Example 7(C).

Analysis %:-

Found:

C, 51.6; H, 6.2; N, 9.2;

Calculated for C₁₉H₂₇N₃O₅S₂:

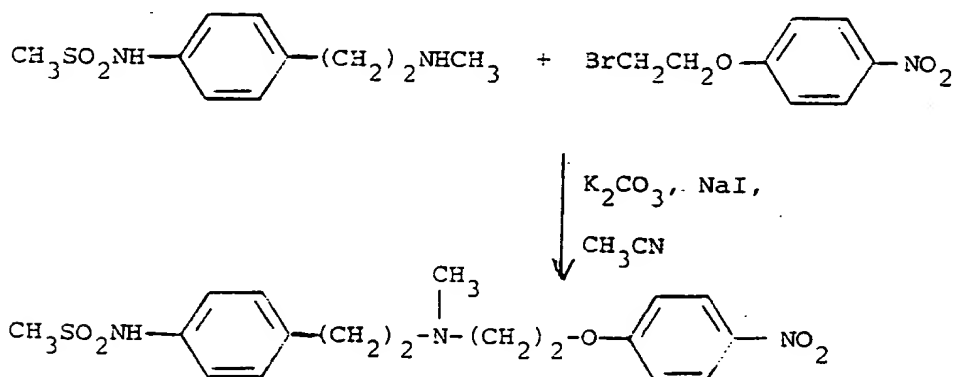
C, 51.9; H, 6.15; N, 9.4.

47

EXPRESS MAIL NO. B 20307523

EXAMPLE 20

(A) 1-(4-Nitrophenoxy)-2-[N-methyl-N-(4-methanesulphonamido-phenethyl)amino]ethane



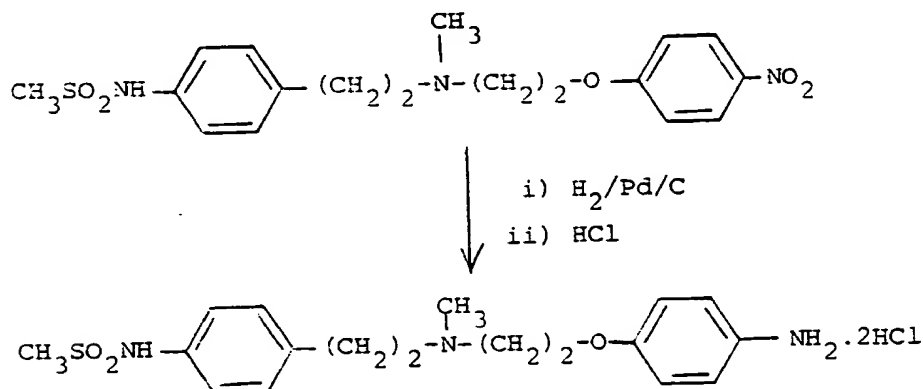
A solution of N-methyl-4-methanesulphonamidophenethylamine (1.0 g) (see Preparation 8), 2-(4-nitrophenoxy)ethyl bromide (1.2 g) (C.A., 54, 11046a), potassium carbonate (0.67 g) and sodium iodide (0.72 g) in acetonitrile (100 ml) was stirred at reflux for 3 days. On evaporation to dryness, the residual oil was partitioned between water and methylene chloride. After two further extractions with methylene chloride, the organic portions were combined, washed with saturated brine solution, dried over anhydrous magnesium sulphate, filtered and evaporated to dryness. The resultant yellow oil was taken up in hot methanol, cooled and the title compound crystallised as a colourless solid, (1.2 g).

N.m.r. (CDCl_3): δ = 2.48 (s, 3H); 2.82 (m, 4H); 2.93 (t, 2H); 3.02 (s, 3H); 4.18 (t, 2H); 6.98 (d, 2H); 7.18 (d, 2H); 7.22 (d, 2H); 8.15 (d, 2H).

48

EXPRESS MAIL B 30304523

(B) 1-(4-Aminophenoxy)-2-[N-methyl-N-(4-methanesulphonamidophenethyl)amino]ethane, dihydrochloride



A solution of 1-(4-nitrophenoxy)-2-[N-methyl-N-(4-methanesulphonamidophenethyl)amino]ethane (1.0 g) in ethanol (50 ml) containing 5% Pd/C (0.1 g) was stirred under a hydrogen atmosphere (50 p.s.i.) for 4 hours. The reaction mixture was then filtered and the solvent evaporated to give a brown oil, which was purified by column chromatography on silica ("Kieselgel 60" - Trade Mark) eluting with methylene chloride. The appropriate fractions were combined and evaporated to give a yellow oil (0.5 g) which was dissolved in ethyl acetate and an ethereal solution of hydrochloric acid added until precipitation was complete. The resultant colourless solid was washed with dry ether to give the title compound, yield 0.35 g, m.p. 220-223°.

Analysis %:-

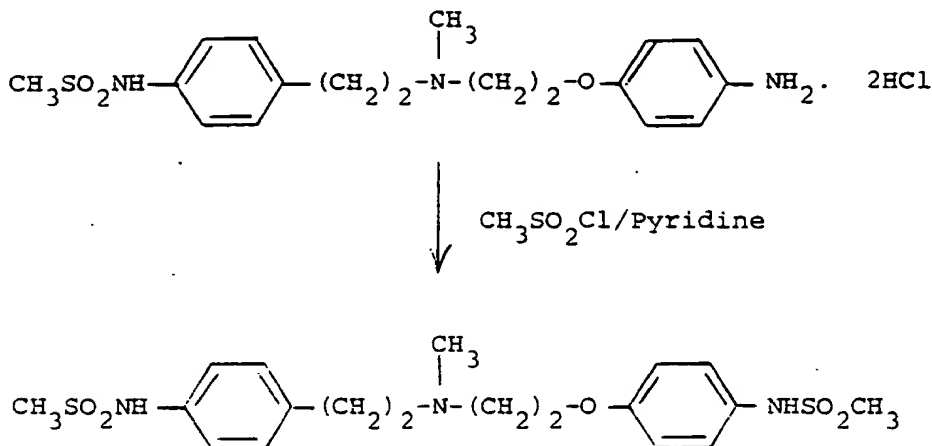
Found:

C, 48.4; H, 6.4; N, 9.0;

Calculated for $\text{C}_{18}\text{H}_{25}\text{N}_3\text{O}_3\text{S} \cdot 2\text{HCl} \cdot \frac{1}{2}\text{H}_2\text{O}$: C, 48.5; H, 6.3; N, 9.4.

EXPRESS MAIL NO. 13 20204523

(C) 1-(4-Methanesulphonamidophenoxy)-2-[N-(4-methanesulphonamidophenethyl)-N-methylamino]ethane



The title compound was prepared by mesylation of 1-(4-aminophenoxy)-2-[N-methyl-N-(4-methanesulphonamidophenethyl)-amino]ethane dihydrochloride hemihydrate (95 mg) with mesyl chloride in pyridine according to the procedure of Example 19(C), yield 30 mg, m.p. 147-149°, confirmed spectroscopically to be identical to the product of Example 7(C).

Analysis %:-

Found:

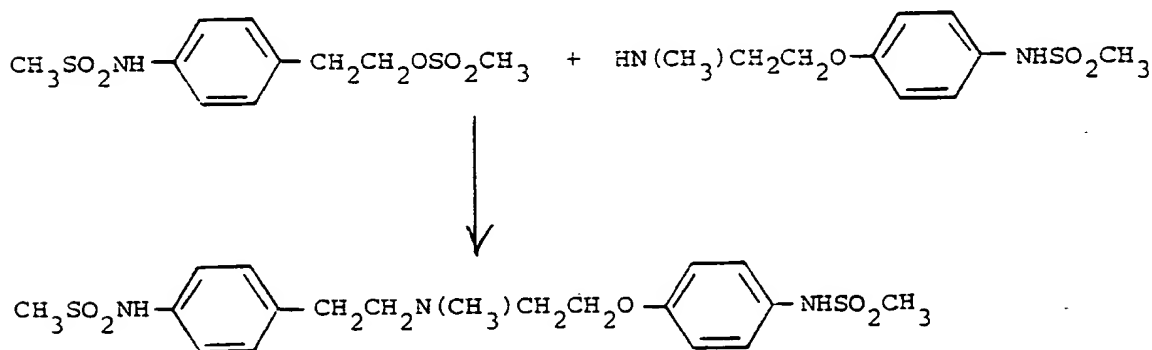
C, 51.6; H, 6.3; N, 9.3;

Calculated for $\text{C}_{19}\text{H}_{27}\text{N}_3\text{O}_5\text{S}_2$:

C, 51.9; H, 6.15; N, 9.4.

EXAMPLE 21

1-(4-Methanesulphonamidophenoxy)-2-[N-(4-methanesulphonamido-phenethyl)-N-methylamino]ethane



A solution of 4-[2-(methanesulphonyloxy)ethyl]methane-
sulphonanilide (0.3 g) and 4-[2-(methylamino)ethoxy]methane-
sulphonanilide (0.38 g) in ethanol (50 ml) was refluxed for 6
hours. On evaporation to dryness the residue was partitioned
between 2N aqueous sodium bicarbonate solution and methylene
chloride. After two further extractions with methylene chloride
the organic portions were combined, washed with saturated brine,
dried over magnesium sulphate, filtered and evaporated to dryness.
The resultant brown oil was chromatographed on silica ("Kieselgel
60" - Trade Mark) eluting with methylene chloride followed by
collection and evaporation of suitable fractions. The resultant
colourless solid was crystallised from ethyl acetate to give the
title compound, (0.21 g), m.p. 150-152°, confirmed spectroscopically
to be identical to the product of Example 7(C).

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Analysis %:-

Found:

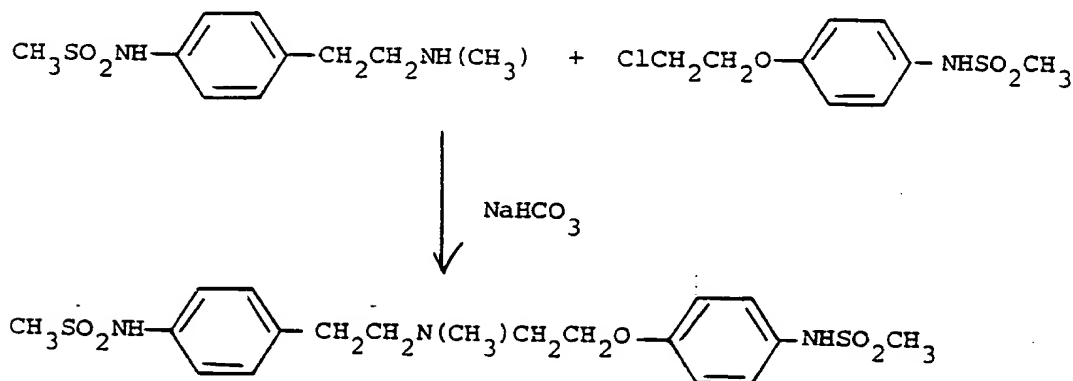
C, 51.6; H, 6.3; N, 9.3.;

Calculated for $C_{19}H_{27}N_3O_5S_2$:

C, 51.9; H, 6.15; N, 9.4.

EXAMPLE 22

1-(4-Methanesulphonamidophenoxy)-2-[N-(4-methanesulphonamidophenyl)-N-methylamino]ethane



A mixture of 4-[2-(methylamino)ethyl]methanesulphonanilide (0.49 g), 4-(2-chloroethoxy)methanesulphonanilide (0.5 g) and sodium bicarbonate (0.17 g) in ethanol (50 ml) was stirred at reflux for 3 days. On evaporation to dryness, the residue was partitioned between 2N aqueous sodium bicarbonate solution and methylene chloride. After two further extractions with methylene chloride the combined organic portions were washed with saturated brine, dried over anhydrous magnesium sulphate, filtered and evaporated to dryness. The resultant oil was chromatographed on

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silica ("Kieselgel 60" - Trade Mark) eluting with methylene chloride followed by collection and evaporation of suitable fractions. The resultant solid was crystallised from ethyl acetate to give the title compound, (0.25 g), m.p. 150-152°, confirmed spectroscopically to be identical to the product of Example 7(C).

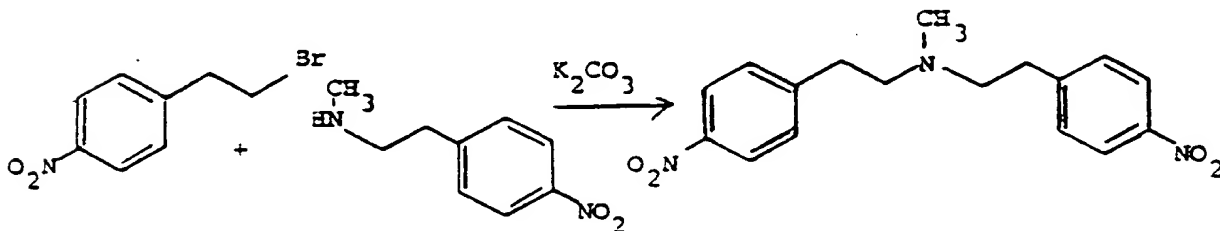
Analysis %:-

Found: C, 52.3; H, 6.3; N, 9.2;

Calculated for $C_{19}H_{27}N_3O_5S_2$: C, 51.9; H, 6.15; N, 9.4.

EXAMPLE 23

(A) N,N-Bis-(4-nitrophenethyl)methylamine



The title compound is a known compound having been isolated as a by-product (7%) from the reaction of 4-nitrostyrene and methylamine. [See Journal Organic Chemistry 1956 Vol. 21 p. 45.] However, it is preferred to make this compound by the route described below.

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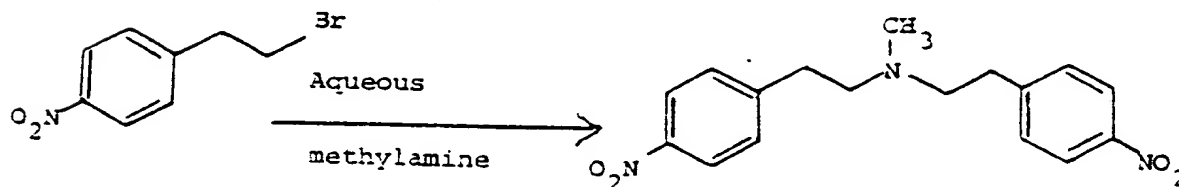
4-Nitrophenethyl bromide (2.6 g, 11.3 mmol), N-methyl-4-nitrophenethylamine (2.0 g, 11.3 mmol) and potassium carbonate (1.6 g, 11.3 mmol) in acetonitrile were stirred at the reflux temperature for 4 days. The solvent was then removed and the residue was taken up in ethyl acetate, washed three times with aqueous sodium carbonate and three times with brine, dried (MgSO_4) and evaporated. The resultant oil was chromatographed on silica eluting with methylene chloride containing methanol (0% up to 2%). The appropriate fractions were combined and evaporated to give an orange oil which was triturated with hexane to give an orange powder which was filtered and dried, yield of the title compound, 1.3 g, m.p. 70-71°.

Analysis %:-

Found: C, 61.7; H, 5.75; N, 12.5;

Calculated for $\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_4$: C, 62.0; H, 5.8; N, 12.8.

Alternative preparation of N,N-bis-(4-nitrophenethyl)methylamine



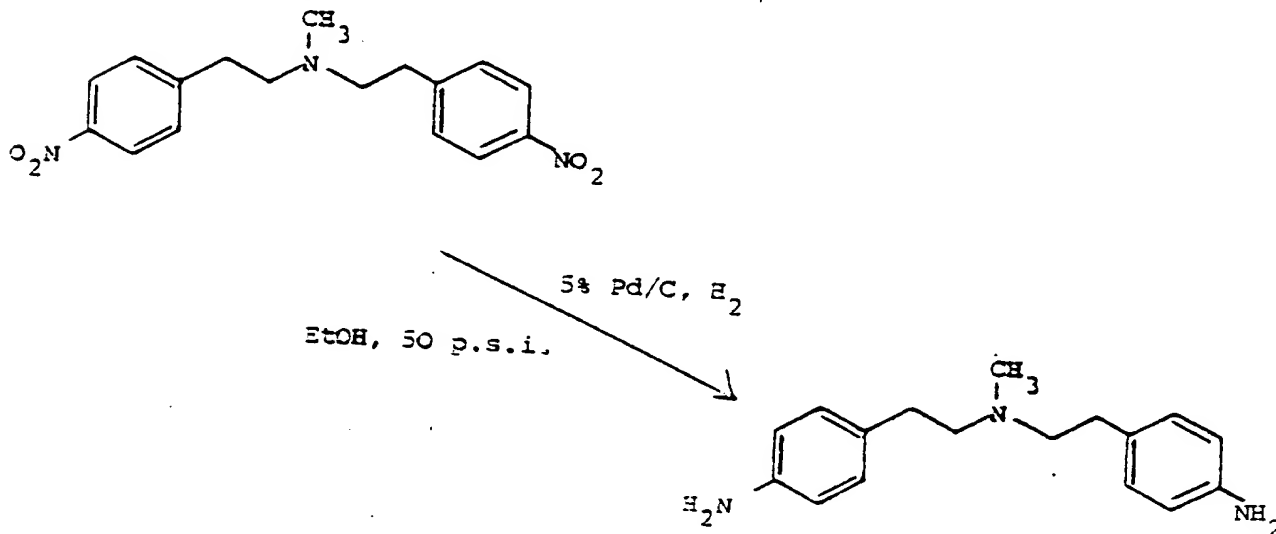
4-Nitrophenethyl bromide (1.0 g, 4.35 mmol) and 33% methylamine in water (10 ml) were stirred together at 55° for 2 hours. The reaction mixture was cooled and the resulting precipitate was collected by filtration and purified by column chromatography on silica eluting with methylene chloride containing methanol (0% up to 5%). The appropriate fractions were combined and evaporated to give the title compound, yield 0.19 g, m.p. 73-75°.

Analysis %:-

Found: C, 62.2; H, 5.9; N, 12.6.

Calculated for $C_{17}H_{19}N_3O_4$: C, 62.0; H, 5.8; N, 12.8.

(B) N,N-Bis(4-aminophenethyl)methylamine



A solution of N,N-bis-(4-nitrophenethyl)methylamine (1.2 g, 3.6 mmol) in ethanol (50 ml) containing 5% Pd/C (0.15 g) was stirred under a hydrogen atmosphere (50 p.s.i.) for 4 hours. The reaction mixture was filtered and the solvent evaporated to give the title compound as an oil, yield 1.0 g, which was used directly without further purification.

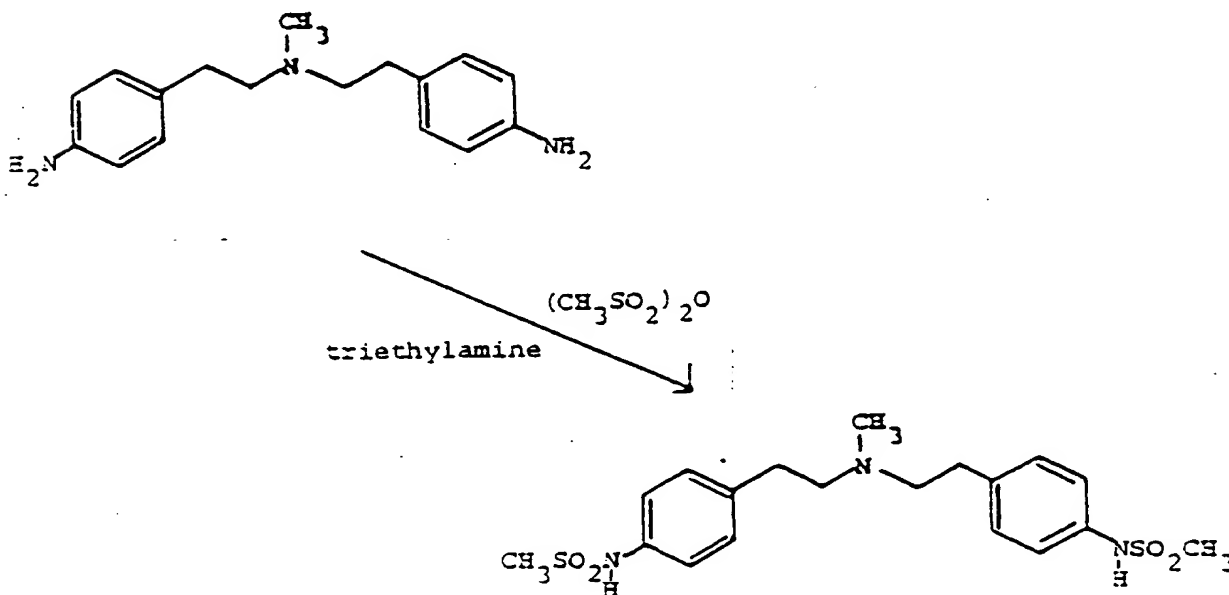
EXPRESS MAIL NO. B 30204523

PK67

N.M.R. (CDCl_3), δ = 6.7 (q, 8H); 3.4 (br s, 4H); 2.6 (s, 8H); 2.3 (s, 3H).

CL

(C) N,N-Bis-(4-methanesulphonamidophenethyl)methylamine



T₁ 560X

P

5 Methanesulphonic anhydride (1.29 g, 7.4 mmole) was added to a solution of *N,N*-bis-(4-aminophenethyl)methylamine (1.0 g, 3.7 mmole) and triethylamine (1 ml, 7.4 mmole) in dry methylene chloride (50 ml) and stirred at room temperature for 2 hours. Methanesulphonic anhydride (1.29 g, 7.4 mmole) was added and the reaction mixture was stirred for a further 2 hours. The solvent

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was removed and the residue was taken up in methylene chloride, washed three times with aqueous sodium bicarbonate and three times with brine, dried (MgSO_4), and evaporated. The resultant oil was chromatographed on silica eluting with methylene chloride containing methanol (0% up to 5%), which after combination and evaporation of the appropriate fractions, gave the title compound, yield 0.29 g, m.p. 170-171°.

Analysis % :-

Found:

C, 53.15; N, 6.5; H, 9.7;

Calculated for $\text{C}_{19}\text{H}_{27}\text{N}_3\text{O}_4\text{S}_2$:

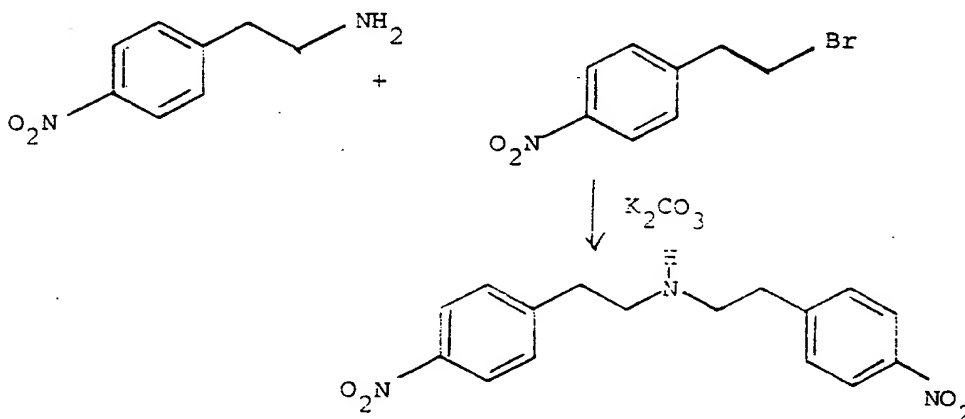
C, 53.6; N, 6.4; H, 9.8*.

N.M.R. (TFAD), δ = 7.1 (q, 8H); 3.5 (m, 4H); 3.3 (m, 4H); 3.0 (s, 6H); 2.95 (s, 3H).

*The sample contained a trace of methylene chloride (1/20 mole CH_2Cl_2 as adjudged by 'H-n.m.r. spectroscopy).

EXAMPLE 24

(A) N-(4-Nitrophenethyl)-4-nitrophenethylamine



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4-Nitrophenethylamine (4 g), 4-nitrophenethyl bromide (5.54 g) and potassium carbonate (3.32 g) were heated under reflux in acetonitrile (50 ml) for 2 days. The solvent was then evaporated, the residue taken up in ethyl acetate and washed three times with aqueous sodium carbonate and three times with brine. The organic phase was dried (Na_2SO_4), filtered and evaporated, and the residual oil was purified by chromatography on silica eluting with methylene chloride containing methanol (0% up to 5%). The product-containing fractions were combined and the solvent evaporated to give a solid which was recrystallised from ethyl acetate/hexane to give the title compound, yield 2.0 g, m.p. 86-91°.

Analysis %:-

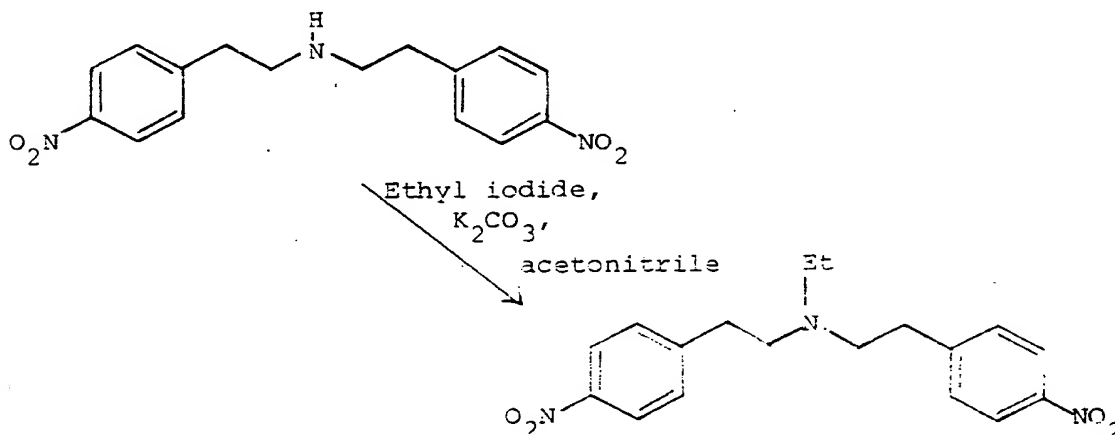
Found:

C, 60.7; H, 5.6; N, 13.1;

Calculated for $\text{C}_{16}\text{H}_{17}\text{N}_3\text{O}_4$:

C, 60.9; H, 5.4; N, 13.3.

(B) N,N-Bis-(4-nitrophenethyl)ethylamine



EXPRESS MAIL NO. B 30204523

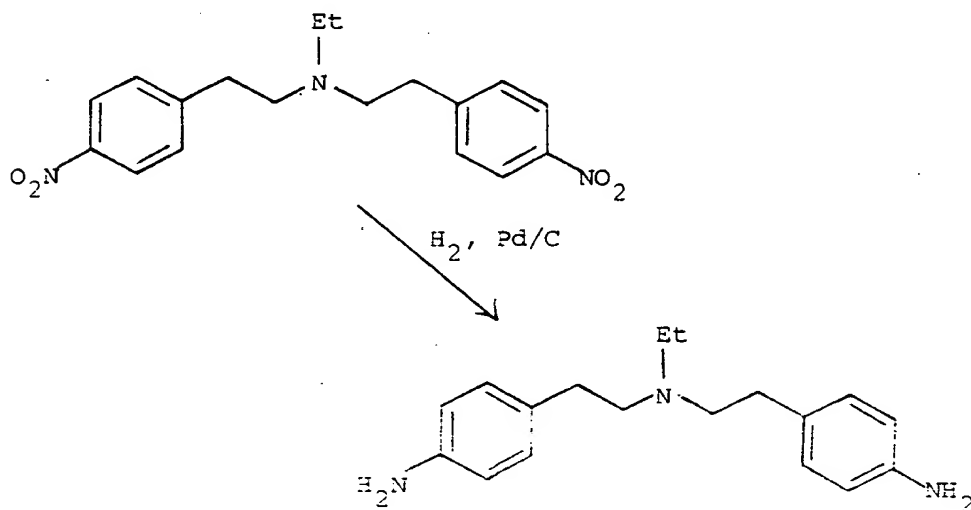
Ethyl iodide (0.37 g) was added dropwise to the product of part (A) (0.75 g) and potassium carbonate (0.33 g) in acetonitrile (20 ml) and the reaction mixture was heated under reflux for 18 hours. The reaction mixture was then evaporated to dryness and the residue taken up in methylene chloride, washed twice with aqueous sodium carbonate, twice with brine, then dried (Na_2SO_4), filtered and evaporated to dryness. The resulting oil was purified by column chromatography on silica eluting with methylene chloride containing methanol (0% up to 2%). The product-containing fractions were combined and evaporated to dryness to give the title compound as an oil, yield 0.47 g.

Analysis %:-

Found: C, 62.7; H, 6.0; N, 12.7;

Calculated for $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_4$: C, 63.0; H, 6.2; N, 12.2.

(C) N,N-Bis-(4-aminophenethyl)ethylamine



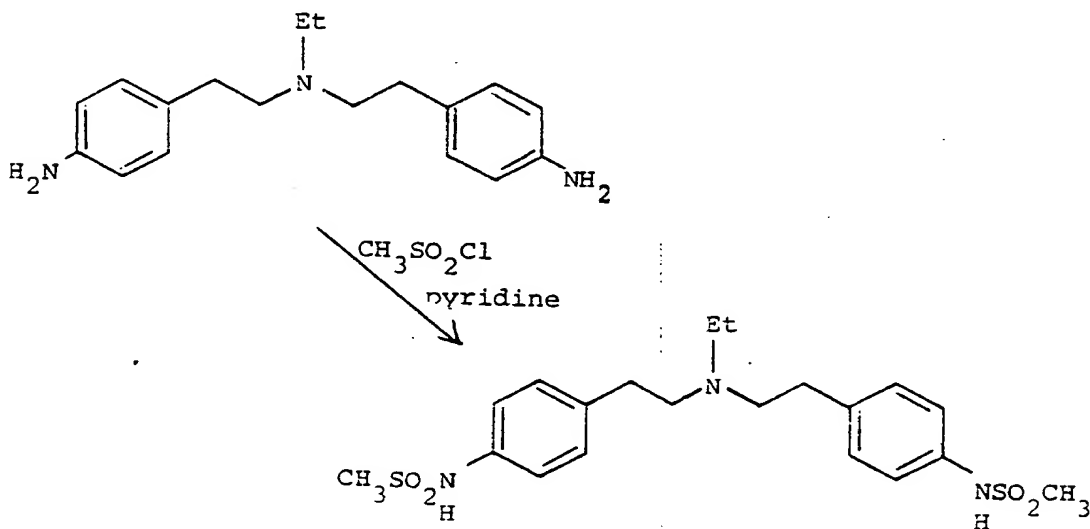
59

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N,N-Bis-(4-nitrophenethyl)ethylamine (0.45 g) was reduced using $H_2/Pd/C$ in a similar fashion to Example 23(B) to provide the title compound, yield 0.32 g.

N.m.r. ($CDCl_3$) δ = 7.05 (d, 2H); 6.7 (d, 2H); 3.55 (broad s, 4H); 2.70 (m, 10H); 1.1 (t, 3H).

(D) N,N-Bis-(4-methanesulphonamidophenethyl)ethylamine



N,N-Bis-(4-aminophenethyl)ethylamine (0.3 g) was acylated with methanesulphonyl chloride in a similar fashion to Example 19(C) to provide the title compound as a foam, yield 0.12 g, m.p. $<60^\circ$.

Analysis %:-

Found:

C, 54.1; H, 6.3; N, 9.2;

Calculated for $C_{20}H_{29}N_3O_4S_2 \cdot 1/4 H_2O$: C, 54.1; H, 6.7; N, 9.5.

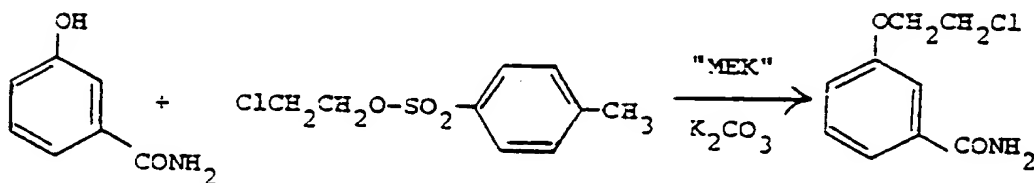
60

EXPRESS MAIL NO. B 20204523

The following Preparations, in which all temperatures are in °C, illustrate the preparation of certain novel starting materials, some of which also form a part of the invention:-

Preparation 1

3-(2-Chloroethoxy)benzamide



To a solution of 3-hydroxybenzamide (21.6 g) in methyl ethyl ketone ("MEK") was added 2-chloroethyl p-toluenesulphonate (55.46 g) and potassium carbonate (16.0 g). After stirring at reflux for 6 hours, the resultant mixture was poured onto water and a colourless solid filtered off. Crystallisation from ethanol gave the title compound, (22.2 g), m.p. 125-126°.

Analysis %:-

Found: C, 53.7; H, 5.3; N, 6.9;
Calculated for C₉H₁₀ClNO₂: C, 54.1; H, 5.05; N, 7.0.

Preparation 2

2-(2-Chloroethoxy)-5-methylbenzamide

The title compound was made similarly to Preparation 1 from corresponding starting materials, m.p. 111-113°.

EXPRESS MAIL NO. B 20204523

Analysis %:-

Found:

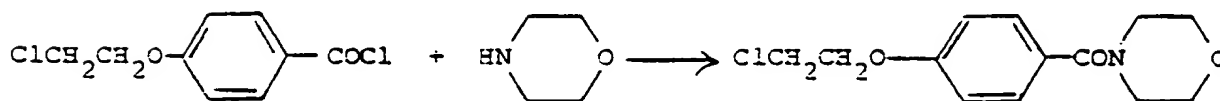
C, 56.4; H, 5.65; N, 6.3;

Calculated for $C_{10}H_{12}ClNO_2$:

C, 56.2; H, 5.7; N, 6.6.

Preparation 3

4-[4-(2-Chloroethoxy)benzoyl]morpholine



4-(2-Chloroethoxy)benzoyl chloride (5.0 g) was dissolved in dry methylene chloride and stirred while cooling to 0°. Morpholine (4.0 g) was added dropwise and the mixture was stirred at room temperature for 2 days. The resultant colourless solid was filtered off and the liquors allowed to stand from which the title compound crystallised (5.5 g), m.p. 102-4°.

Analysis %:-

Found:

C, 58.1; H, 6.0; N, 5.25;

Calculated for $C_{13}H_{16}ClNO_3$:

C, 57.9; H, 6.0; N, 5.2.

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Preparation 4

N,N-Diethyl 4-(2-chloroethoxy)benzamide

The title compound was prepared similarly to the previous Preparation from corresponding starting materials, m.p. 80-81°.

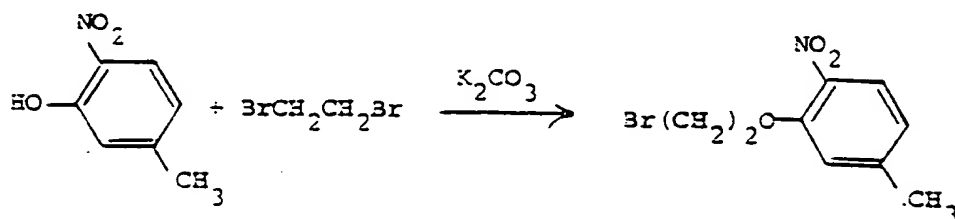
Analysis %:-

Found: C, 60.8; H, 7.0; N, 5.3;

Calculated for $C_{12}H_{18}ClNO_2$: C, 61.05; H, 7.1; N, 5.5.

Preparation 5

5-Methyl-2-nitrophenyl 2'-bromoethyl ether



10

5-Methyl-2-nitrophenol (5.0 g) and potassium carbonate (4.6 g) in butanone (100 ml) were stirred together at room temperature for 0.5 hours. 1,2-Dibromoethane (3.1 g) was then added and the mixture stirred at reflux for 2 days. After evaporation to dryness, distilled water was added and the mixture

15 was extracted three times with methylene chloride. The combined organic liquors were washed with water, dried over magnesium sulphate, filtered and evaporated to give a yellow solid which was

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EXPRESS MAIL NO. B 20204533

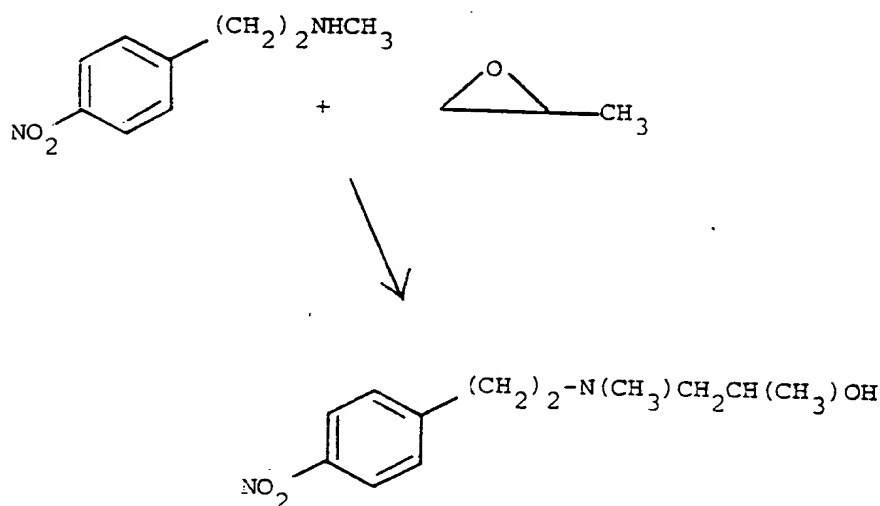
removed by filtration and the solution was evaporated to low bulk,
giving the title compound as colourless crystals, m.p. 48-49°,
used in Example 10.

N.m.r. (CDCl₃), ppm δ = 7.8 (d, 1H); 6.9 (m, 2H); 4.42 (t, 2H);
3.7 (t, 2H); 2.45 (s, 3H).

3-Nitrophenyl 2'-bromoethyl ether and 2-nitrophenyl
2'-bromoethyl ether used, respectively, as starting materials in
Examples 8 and 9 are known compounds [see J. Med. Chem., (1970),
13(6), 1149 and C.A., 61, 601a].

Preparation 6

(A) 1-[N-Methyl-N-(4-nitrophenethyl)amino]-2-hydroxypropane

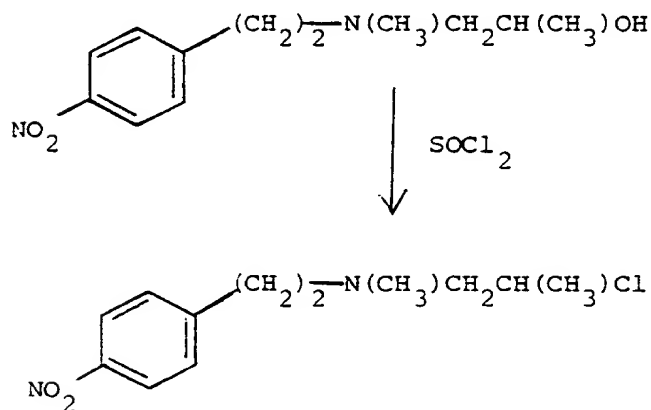


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A solution of N-methyl-4-nitrophenethylamine (1.8 g) and propylene oxide (0.66 g) in ethanol (50 ml) was stirred at reflux for 5 hours. After evaporation to dryness the residual orange oil was chromatographed on silica ("Kieselgel 60" - Trade Mark) eluting with ethyl acetate followed by collection and evaporation of suitable fractions to give the title compound as a yellow oil.

N.m.r. (CDCl_3) p.p.m., δ = 1.1 (d, 3H); 2.3 (m, 2H); 2.32 (s, 3H); 2.75 (m, 2H); 2.9 (m, 2H); 3.15 (broad, 1H); 3.72 (m, 1H); 7.15 (d, 2H); 8.18 (d, 2H).

(B) 1-[N-Methyl-N-(4-nitrophenethyl)amino]-2-chloropropane



Thionyl chloride (50 ml) was added dropwise with stirring and cooling in an ice/water bath to 1-(N-methyl-N-(4-nitrophenethyl)amino)-2-hydroxypropane (1.5 g). After stirring at room temperature for 1 hour, the solution was refluxed on a steam bath

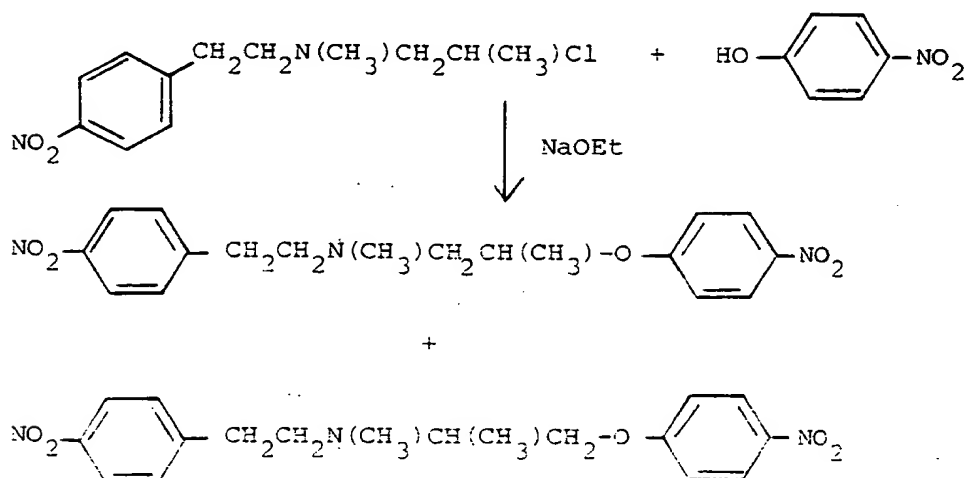
65

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for a further 2 hours. The solution was evaporated to dryness and the residual oil partitioned between 2N aqueous sodium carbonate solution and ethyl acetate. After two further extractions with ethyl acetate, the organic portions were combined, washed with a saturated brine solution, dried over anhydrous magnesium sulphate, filtered and evaporated to dryness. The resultant brown oil was chromatographed on silica ("Kieselgel 60" - Trade Mark) eluting with ethyl acetate followed by collection and evaporation of suitable fractions to give the title compound as a yellow oil, (0.75 g).

N.m.r. (CDCl_3), p.p.m. δ = 1.48 (d, 3H); 2.35 (s, 3H); 2.75 (m, 6H); 4.02 (q, 1H); 7.4 (d, 2H); 8.18 (d, 2H).

(C) 1-[N-methyl-N-(4-nitrophenethyl)amino]-2-(4-nitrophenoxy)propane and 2-[N-methyl-N-(4-nitrophenethyl)amino]-1-(4-nitrophenoxy)propane



66

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P To a solution of sodium (0.075 g) in ethanol (50 ml) was added 4-nitrophenol (0.41 g) and the solution was stirred at room temperature for 1 hour. 1-[N-Methyl-N-(4-nitrophenethyl)amino]-2-chloropropane (0.75 g) was added and the solution stirred at
5 reflux for 3 days. The solution was then evaporated to dryness and the residual oil partitioned between water and methylene chloride. After two further extractions with methylene chloride, the organic portions were combined, washed with a saturated brine solution, dried over anhydrous magnesium sulphate, filtered and
10 evaporated to dryness. The resultant orange oil (1.0 g) was chromatographed on silica ("Kieselgel 60" - Trade Mark) eluting with 1:1 hexane:ethyl acetate.

Collection and evaporation of the least polar product fractions gave the first-named title compound as a yellow oil,
15 (0.25 g).

PH67 N.m.r. (CDCl_3) p.p.m.: δ = 1.3 (d, 3H); 2.4 (s, 3H); 2.75 (m, 6H); 4.58 (q, 1H); 6.91 (d, 2H); 7.35 (d, 2H); 8.1 (d, 2H); 8.2 (d, 2H).

Collection and evaporation of the more polar product
20 fractions gave the second-named title compound as a yellow solid, (0.3 g), which was again characterised by n.m.r. spectroscopy.

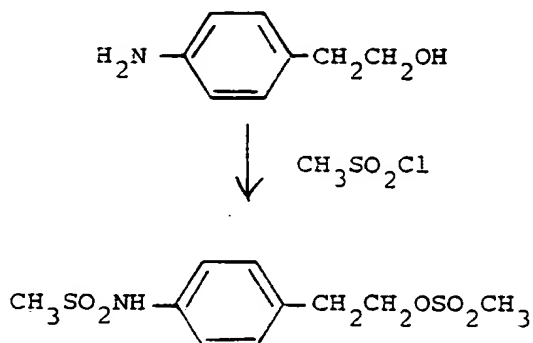
PH67 N.m.r. (CDCl_3) p.p.m.: δ = 1.1 (d, 3H); 2.4 (s, 3H); 2.85 (m, 4H); 3.2 (q, 1H); 3.95 (m, 2H); 6.92 (d, 2H); 7.35 (d, 2H); 8.12 (d, 2H); 8.2 (d, 2H).

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Preparation 7

4-[2-(Methanesulphonyloxy)ethyl]methanesulphonanilide



Methanesulphonyl chloride (50 ml) was added dropwise over 0.5 hours to a stirred solution of 4-aminophenethyl alcohol (41.15 g) in pyridine (350 ml) at 0°. The mixture was allowed to warm to room temperature and stirred overnight. The mixture was then poured onto water (700 ml) from which an orange solid crystallised. After filtration, the solid was dissolved in methylene chloride, dried over magnesium sulphate, filtered and the filtrate re-evaporated. Crystallisation of the resultant solid from ethyl acetate gave the title compound, (45.5 g), m.p. 136-137°.

Analysis %:-

Found:

C, 40.6; H, 5.2; N, 4.9;

Calculated for $\text{C}_{10}\text{H}_{15}\text{NO}_5\text{S}_2$:

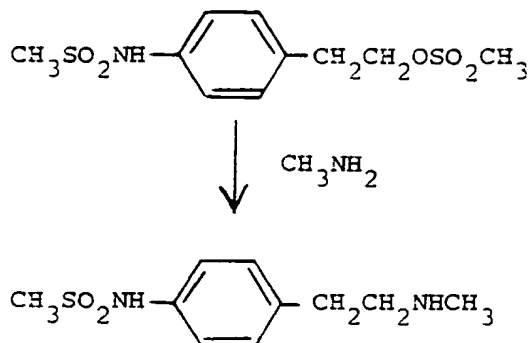
C, 40.9; H, 5.15; N, 4.8.

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EXPRESS MAIL NO. B 20204523

Preparation 8

4-[2-(Methylamino)ethyl]methanesulphonanilide



To a solution of 4-[2-(methanesulphonyloxy)ethyl]methane-
sulphonanilide (10.3 g) in ethanol (20 ml) was added a solution of
5 methylamine in industrial methylated spirits (30 ml of 33%
solution). The mixture was heated with stirring at 85° in a
pressure vessel for 17 hours. After cooling, the resultant
solution was evaporated to dryness, the residue dissolved in
water, and the resultant solution basified by the addition of
10 sodium hydroxide (1.4 g) in water (12 ml). Evaporation gave an
off-white solid which was chromatographed on silica ("Kieselgel
60" - Trade Mark) eluting with methylene chloride/methanol (3:1).
Collection and evaporation of suitable fractions gave an off-white
solid (4.8 g) which crystallised from ethyl acetate/methanol to
14 15 give the title compound, (1.8 g), m.p. 133-135°.

EXPRESS MAIL NO. B 30204523

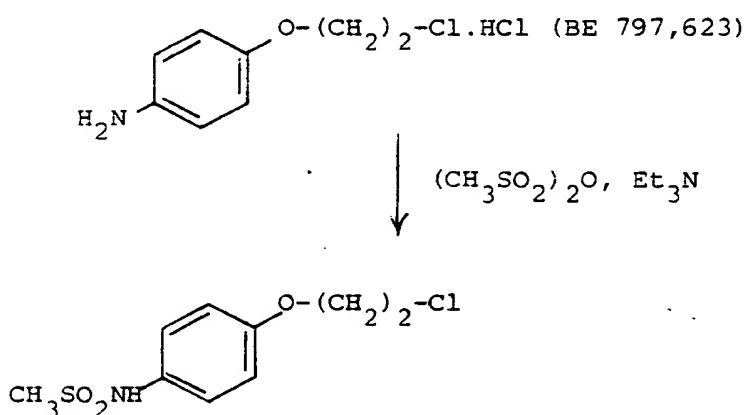
Analysis %:-

Found: C, 52.5; H, 7.1; N, 12.2;

Calculated for $C_{10}H_{16}N_2O_2S$: C, 52.6; H, 7.1; N, 12.3.

Preparation 9

5 4-(2-Chloroethoxy)methanesulphonanilide



To a solution of 4-(2-chloroethoxy)aniline hydrochloride (9.5 g) and methanesulphonic anhydride (12.0 g) in methylene chloride (100 ml) was added dropwise with cooling, triethylamine (25 ml) and the mixture was stirred at room temperature overnight.

10 The resultant mixture was partitioned between 2N aqueous sodium bicarbonate solution and methylene chloride. After two further extractions with methylene chloride, the organic portions were combined, dried over magnesium sulphate, filtered and evaporated to dryness. The resultant solid (9.5 g) was crystallised from

15 methanol after filtration of impurity to give the title compound as slightly pink crystals, (5.6 g), m.p. 111-114°.

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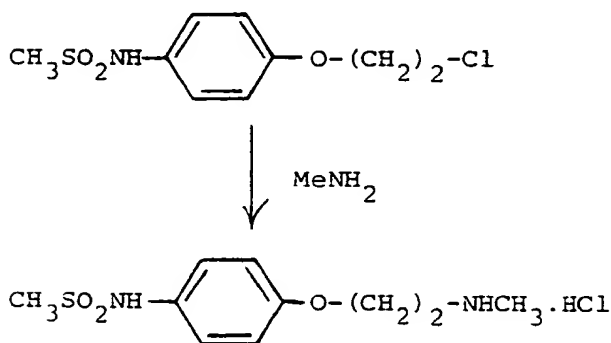
14 67

N.m.r. (CDCl₃) p.p.m.: δ = 2.84 (s, 3H); 3.8 (t, 2H); 4.2 (t, 2H); 6.75 (d, 2H); 7.15 (d, 2H); 9.0 (broad s, 1H).

CL
L

Preparation 10

4-[2-(Methylaminoethoxy)]methanesulphonanilide hydrochloride



T, 710X

P 5

A suspension of 4-(2-chloroethoxy)methanesulphonanilide (12.7 g) in a solution of methylamine in industrial methyated spirits (160 ml of 33%) was heated with stirring at 100° in a pressure vessel overnight. After cooling the resultant dark solution was evaporated to dryness. Crystallisation of the residue from ethanol gave the title compound as a colourless solid, (10.1 g), m.p. 192-194°.

10

14

Analysis %:-

Found:

C, 42.9; H, 6.0; N, 9.9;

Calculated for C₁₀H₁₆N₂O₃S.HCl: C, 42.8; H, 6.1; N, 10.0.

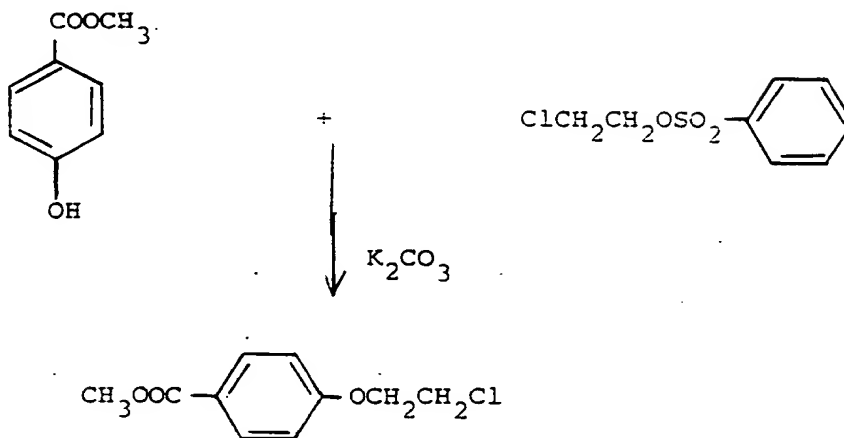
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2
H

71

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Preparation 11

Methyl 4-(2-chloroethoxy)benzoate



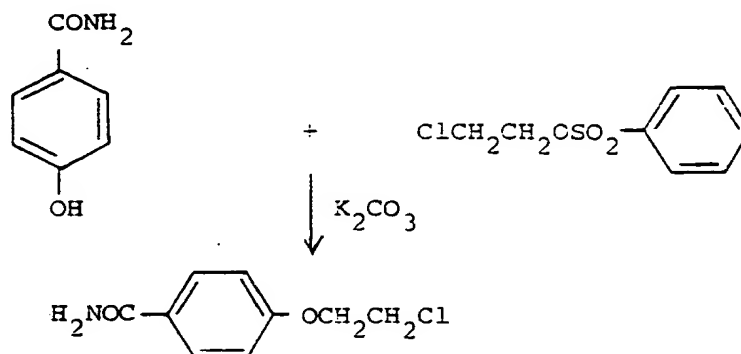
A mixture of methyl 4-hydroxybenzoate (15.2 g, 0.1 M),
 2-(benzenesulphonyloxy)ethyl chloride (28.65 g, 0.12 M) and
 potassium carbonate (19.15 g, 0.1 M) in 4-methylpentan-2-one (170
 ml) was stirred at reflux for 24 hours. After cooling, distilled
 water (170 ml) was added and the organic phase separated off.
 Evaporation to dryness gave a yellow solid which was crystallised
 from ethanol to give the title compound, yield (13.3 g), m.p.
 56-58°.

N.m.r. (CDCl₃) δ = 8.02 (d, 2H); 6.96 (d, 2H); 4.3 (t, 2H); 3.92
 (s, 3H); 3.88 (t, 2H).

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Preparation 12

4-(2-Chloroethoxy)benzamide



A mixture of 4-hydroxybenzamide (194 g, 1.25 M), 2-(benzenesulphonyloxy)ethyl chloride (359 g, 1.8 M), and potassium carbonate (172.8 g, 1.25 M) in butan-2-one (2.16 l) was stirred at reflux for 24 hours. After cooling, distilled water (2.0 l) was added and the resultant precipitate filtered off, washed with water, and dried. Crystallisation from ethanol gave the title compound, yield (232.0 g), m.p. 66°.

Analysis %:-

Found:

C, 54.2; H, 5.0; N, 6.9;

Calculated for $C_{10}H_{11}ClO_3$:

C, 54.25; H, 5.1; N, 7.0.

2M We claim:

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